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DENGUE, CHIKUNGUNYA ET MALADIE A VIRUS ZIKA

Smartphone multiplex microcapillary diagnostics using Cygnus: Development and evaluation of rapid serotype-specific NS1 detection with dengue patient samples.

Needs, S., Sirivisoot, S., Jegouic, S., Prommool, T., Luangaram, P., Srisawat, C., Sriraksa, K., Limpitikul, W., Mairiang, D., Malasit, P., Avirutnan, P., Puttikhunt, C., Edwards, A.
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Laboratory diagnosis of dengue virus (DENV) infection including DENV serotyping requires skilled labor and well-equipped settings. DENV NS1 lateral flow rapid test (LFT) provides simplicity but lacks ability to identify serotype. A simple, economical, point-of-care device for serotyping is still needed. We present a gravity driven, smartphone compatible, microfluidic device using microcapillary film (MCF) to perform multiplex serotype-specific immunoassay detection of dengue virus NS1. A novel device-termed Cygnus-with a stackable design allows analysis of 1 to 12 samples in parallel in 40 minutes. A sandwich enzyme immunoassay was developed to specifically detect NS1 of all four DENV serotypes in one 60-µl plasma sample. This test aims to bridge the gap between rapid LFT and laboratory microplate ELISAs in terms of sensitivity, usability, accessibility and speed. The Cygnus NS1 assay was evaluated with retrospective undiluted plasma samples from 205 DENV infected patients alongside 50 febrile illness negative controls. Against the gold standard RT-PCR, clinical sensitivity for Cygnus was 82% in overall (with 78, 78, 80 and 76% for DENV1-4, respectively), comparable to an in-house serotyping NS1 microplate ELISA (82% vs 83%) but superior to commercial NS1-LFT (82% vs 74%). Specificity of the Cygnus device was 86%, lower than that of NS1-microplate ELISA and NS1-LFT (100% and 98%, respectively). For Cygnus positive samples, identification of DENV serotypes DENV2-4 matched those by RT-PCR by 100%, but for DENV1 capillaries false positives were seen, suggesting an improved DENV1 capture antibody is needed to increase specificity. Overall performance of Cygnus showed substantial agreement to NS1-microplate ELISA (κ = 0.68, 95%CI 0.58-0.77) and NS1-LFT (κ = 0.71, 95%CI 0.63-0.80). Although further refinement for DENV-1 NS1 detection is needed, the advantages of multiplexing and rapid processing time, this Cygnus device could deliver point-of-care NS1 antigen testing including serotyping for timely DENV diagnosis for epidemic surveillance and outbreak prediction.

Knowledge, attitudes, practices and perceptions about Zika in women of childbearing age in Amazonas, Peru.

Mateo, S., Guzmán-Cuzcano, J., Peña-Sánchez, E., Yon, C., Valderrama, B., Carrasco, J., La Torre, L., Chapilliquen, F., Aguilar, M., Quezada, E., Pershing Bustamante, T.
01-04-2022
Rev Peru Med Exp Salud Publica
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To describe the knowledge, attitudes, practices, and perceptions about Zika in women of childbearing age (WCA) in the department of Amazonas in Peru, following a Zika outbreak. Descriptive study with a mixed quantitative-qualitative approach. We carried out stratified sampling, by applying a survey to a sample of 723 WCA aged 15 to 49 years in the district of Bagua, department of Amazonas, then we carried out four focus groups with 35 WCA in each group. Frequencies and the grounded theory were used for quantitative and qualitative analysis respectively. Interpretation of both methods was integrated using a narrative approach. We found that 86.3% of WCA knew that it is possible to get sick with Zika, 10.1% knew that it is transmitted through sexual intercourse, 2.2% knew that it can be transmitted during pregnancy and 68.5% consider that the information is insufficient. In practice, 60% (n=434) used mosquito nets, 53.4% (n=386) covered water containers and 7.3% (n=4) perceived local government involvement. Qualitative data showed distrust of vector control and expressed the need for psychological support for pregnant women and their families. There are gaps in the knowledge and practices of WCA regarding the prevention of sexual and vertical transmission of Zika; WCA distrust vector control, do not perceive local government involvement, suggest psychological support should be provided to pregnant women with Zika, as well as to mothers with disabled children, and wish to access more information about Zika.

[ARBOALVO: territorial stratification for definition of areas for prompt response by surveillance and timely control of urban arbovirus infections].

Santos, J., Albuquerque, H., Siqueira, A., Praça, H., Pereira, L., Tavares, A., Gusmão, E., Bruno, P., Barcellos, C., Carvalho, M., Sabroza, P., Honório, N.
01-04-2022
Cad Saude Publica
https://pubmed.ncbi.nlm.nih.gov/35384994

The study aimed to present the methodological proposal entitled "Prompt Response", modelled in the cities of Belo Horizonte (Minas Gerais State) and Natal (Rio Grande do Norte State), Brazil. The proposal aims to identify and demarcate priority areas for timely targeting of surveillance activities, aiming to reduce the intensity and velocity in the spread of epidemics in endemic urban areas. The methodology uses three variables that represent the necessary causes for the production and reproduction of dengue: notified cases (virus), Aedes eggs (vector), and population (host). This was an ecological study that used data from three information planes aggregated in finer temporal and spatial scales of 3 to 4 weeks and 400 to 600-meter grids, respectively. The prompt response areas were defined by Scan statistical analysis with definition of simultaneous spatial

clusters for the three planes via the SaTScan program. In Natal, the areas defined as prompt response occupied, on average, 15.2% of the city's territory and concentrated 67.77% of the dengue cases in the period following demarcation of the prompt response areas. In Belo Horizonte, the observed proportions were 64.16% of cases in 23.23% of the territory. These results were obtained in two cities with different socioenvironmental and geographic realities and distinct epidemiological profiles, indicating that the methodology can be applied to different urban realities, allowing control programs to concentrate on reduced portions of the territory and impacting a high percentage of cases in timely fashion.

Spatio-temporal dynamics of dengue-related deaths and associated factors.

Santana, L., Baquero, O., Maeda, A., Nogueira, J., Chiaravalloti Neto, F.
04-04-2022
Rev Inst Med Trop Sao Paulo
https://pubmed.ncbi.nlm.nih.gov/35384961

Since the reintroduction of dengue viruses in 1987, Sao Paulo State (SP), Brazil, has experienced recurrent epidemics in a growing number of municipalities, each time with more cases and deaths. In the present study, we investigated the spatio-temporal dynamics of dengue-related deaths and associated factors in SP. This was an ecological study with spatial and temporal components, based on notified dengue-related deaths in the municipalities of SP between 2007 and 2017. A latent Gaussian Bayesian model with Poisson probability distribution was used to estimate the standardized mortality ratios (SMR) for dengue and relative risks (RR) for the socioeconomic, demographic, healthcare-related, and epidemiological factors considered. Epidemiological factors included the annual information on the number of circulating serotypes. A total of 1,019 dengue-related deaths (0.22 per 100,000 inhabitant-years) between 2007 and 2017 were confirmed in SP by laboratory testing. Mortality increased with age, peaking at 70 years or older (1.41 deaths per 100,000 inhabitant-years). Mortality was highest in 2015, and the highest SMR values were found in the North, Northwest, West, and coastal regions of SP. An increase of one circulating serotype, one standard deviation in the number of years with cases, and one standard deviation in the degree of urbanization were associated with increases of 75, 35, and 45% in the risk of death from dengue, respectively. The risk of death from dengue increased with age, and the distribution of deaths was heterogeneous in space and time. The positive relationship found between the number of dengue serotypes circulating and years with cases at the municipality/micro-region level indicates that this information can be used to identify risk areas, intensify surveillance and control measures, and organize healthcare to better respond to this disease.

Silent circulation of Chikungunya virus among pregnant women and newborns in the Western Brazilian Amazon before the first outbreak of chikungunya fever.

Kanunfre, K., Rocha, M., Malta, M., Souza, R., Castro, M., Boscardin, S., Souza, H., Witkin, S., Cardoso, M., Okay, T.
04-04-2022
Rev Inst Med Trop Sao Paulo
https://pubmed.ncbi.nlm.nih.gov/35384956

The prevalence of immunity to Chikungunya virus (CHIKV) in pregnant women and newborns in the Western Brazilian Amazon was assessed at a time when previous studies did not report chikungunya fever in the area. In 435 asymptomatic pregnant women and 642 healthy unrelated newborns, the presence of IgM and IgG antibodies to CHIKV were determined by a commercial ELISA. All participants were negative to IgM anti-CHIKV. Anti-CHIKV IgG was identified in 41 (9.4%) pregnant women and 66 (10.3%) newborns. The presence of anti-CHIKV IgG was positively associated with the lowest socioeconomic status in pregnant women (OR 2.54, 95% CI 1.15-5.62, p=0.021) and in the newborns' mothers (OR 5.10, 95% CI 2.15-12.09, p< 0.001). Anti-CHIKV IgG was also associated with maternal age in both, the pregnant women (OR 1.06, 95% CI 1.00-1.11, p=0.037) and the newborns'mothers (OR 1.08, 95% CI 1.03-1.12, p=0.001). Pregnancy outcomes in which the mother or the newborn was anti-CHIKV IgG positive proceeded normally. Negative CHIKV serology was associated with being positive for DENV antibodies and having had malaria during pregnancy. These findings showed that there was already a silent circulation of CHIKV in this Amazon region before the first outbreak of chikungunya fever. Furthermore, seropositivity for CHIKV was surprisingly frequent (10%) in both, pregnant women and newborns, affecting mainly low-income women.

Clinical and Haematological Findings in Dengue Fever.

Razi, R., Ahmed, A., Sultana, S., Amin, K., Ahsan, M., Akter, P., Paul, P., Sangma, M., Ferdousi, R., Jahan, F., Hasan, M., Ahsan, S.
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Mymensingh Med J
https://pubmed.ncbi.nlm.nih.gov/35383748

From 2000 onwards dengue fever has been occurring at regular intervals in Bangladesh. Ultrasonography is a useful diagnostic procedure. This study was done, keeping this background in mind. Objective of this study was to identify the role of ultrasonography as a useful tool in early diagnosis of dengue haemorrhagic fever. This was a cross-sectional descriptive type of observational study. Results of ultrasonography, haematogy an immunology were observed in 2004 and 2019 in 32 patients on each occasion. In 2004 out of 32 patients 29 had positive ultrsonographic findings supported by corresponding haematological and immunological findings. In 2019 ultrsonography was done in three out of thirty two patients, all three had had positive

ultra sonographic findings which were supported by haematological and immunological findings. Dengue fever has serious complications like plasma leakage which manifest in the form of ascites, pleural effusion, thick gallbladder wall etc. If such complications can be detected at an early stage many lives can be saved.

Fertility decision-making during the Zika virus epidemic in Brazil: Where is the decision?

Stolow, J., Kendall, C., Marto Leal Pinheiro, F., Campos da Rocha Feitosa, M., Alves de Almeida Furtado, K., Ferreira Martins, A., Paz Albino Dos Santos, M., Ecilda Lima Ellery, A., Dias, L., Cristina de Holanda Barreto, I., Moses, L., Castro, A., Dunn, C., Kerr, L.
31-03-2022
Sex Reprod Healthc
https://pubmed.ncbi.nlm.nih.gov/35381437

In 2016, a Public Health Emergency of International Concern (PHEIC) was declared in response to the rise of microcephaly cases among newborns in Northeastern Brazil. A common reactionary measure by public health authorities was to recommend women postpone pregnancy to avoid the possible perinatal transmission of Zika virus (ZIKV). The purpose of this study was to assess how women in Fortaleza, Brazil conceptualize pregnancy; experience facilitators and barriers to pregnancy avoidance; perceive the authorities' recommendation to postpone pregnancy due to the ZIKV outbreak; and recall their experiences during the ZIKV epidemic. Qualitative methods, specifically a Rapid Anthropological Assessment (RAA), were utilized in this study. Data collection included semi-structured interviews, triangulated with observations and informal interviews with community members. The sample included 35 women (18-39 years old) who exclusively utilized the national public health care system. Findings indicated that all participants perceived the ZIKV pregnancy-postponement recommendation to be counter-cultural to Brazilian social norms. Overall women's self-perceived agency to prevent pregnancy was low due to social expectations and lack of trust for contraceptives. ZIKV prevention was not seen as a reason to utilize contraceptives. Interestingly, only women who self-perceived as more affluent were willing to attempt pregnancy prevention for educational, occupational, or financial opportunity. Pregnancy postponement as a response to a ZIKV epidemic ignores gaps in reproductive agency and defies social norms, making it unrealistic and counter-cultural. Future ZIKV health recommendations must be culturally aligned with the population, and address barriers and motivators for family planning.

A mathematical model to describe antibody-dependent enhancement and assess the effect of limiting cloning for plasma cells in heterologous secondary dengue infection.

Alves Rubio, F., Mo Yang, H.
03-04-2022
Math Med Biol
https://pubmed.ncbi.nlm.nih.gov/35380162

We propose a mathematical model to study the antibody-dependent enhancement (ADE) phenomenon. Here, we explore the interaction between macrophages, dengue virus and plasma cells, especially the effect of a limitation on plasma cell proliferation, which occurs due to immunological memory. The model has up to three equilibrium points: one virus-free equilibrium and two virus-presence equilibrium, depending on the value of two thresholds. We determine the existence regions for the model equilibrium points and their stability, a sensitivity analysis was performed in the model thresholds. Numerical simulations illustrate that ADE can occur even when the basic reproduction number is less than one.

Zika virus vertical transmission in interferon receptor1-antagonized Rag1$^{-/-}$ mice results in postnatal brain abnormalities and clinical disease.

Winkler, C., Clancy, C., Rosenke, R., Peterson, K.
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Acta Neuropathol Commun
https://doi.org/10.1186/s40478-022-01351-6

The mechanisms by which vertically transmitted Zika virus (ZIKV) causes postnatal brain development abnormalities and congenital disease remain poorly understood. Here, we optimized the established anti-IFNAR1 treated, Rag1$^{-/-}$ (AIR) mouse model of ZIKV infection to examine the consequence of vertical transmission on neonate survival and postnatal brain development. We found that modulating the infectious dose and the frequency of anti-IFNAR1 treatment of pregnant mice (termed AIR^{low} mice) prolonged neonatal survival allowing for pathogenesis studies of brain tissues at critical postnatal time points. Postnatal AIR^{low} mice all had chronic ZIKV infection in the brain that was associated with decreased cortical thickness and cerebellar volume, increased gliosis, and higher levels of cell death in many brain areas including cortex, hippocampus and cerebellum when compared to controls. Interestingly, despite active infection and brain abnormalities, the neurodevelopmental program remained active in AIR^{low} mice as indicated by elevated mRNA expression of critical neurodevelopmental genes in the brain and enlargement of neural-progenitor rich regions of the cerebellum at a developmental time point analogous to birth in humans. Nevertheless, around the developmental time point when the brain is fully populated by neurons, AIR^{low} mice developed neurologic disease associated with persistent ZIKV infection in the brain, gliosis, and increased cell death. Together, these data show that vertically transmitted ZIKV infection in the brain of postnatal AIR^{low} mice strongly influences brain development resulting in structural abnormalities and cell death in multiple regions of the brain.

PD1 CD44 Antiviral Peptide as an Inhibitor of the Protein-Protein Interaction in Dengue Virus Invasion.

Recalde-Reyes, D., Rodríguez-Salazar, C., Castaño-Osorio, J., Giraldo-Giraldo, M.
01-04-2022
Peptides
https://pubmed.ncbi.nlm.nih.gov/35378215

Dengue virus (DENV) infection is mediated by the interaction between the virus envelope protein and cellular receptors of the host cells. In this study, we designed peptides to inhibit protein-protein interaction between dengue virus and CD44 receptor, which is one of the receptors used by DENV for entry. In silico model complexes were designed between domain III of the viral envelope protein of dengue virus 2 and the domain of human CD44 receptor using ClusPro 2.0, (https://cluspro.bu.edu/login.php), and inhibition peptides were designed with Rosetta Online-Server(http://rosie.rosettacommons.org/peptiderive). We identified one linear antiviral peptide of 18 amino acids derived from the human CD44 receptor, PD1 CD44. It did not show hemolysis or toxicity in HepG2 or BHK cell lines, nor did it stimulate the release of IL-1β, IL-6, TNF-α, and IFN-γ, below 100µM. It had an IC50 of 13.8µM and maximum effective dose of 54.9µM evaluated in BHK cells. The decrease in plaque-forming units/mL for DENV1, DENV2, DENV3, and DENV4 was 99.60%, 99.40%, 97.80%, and 70.50%, respectively, and similar results were obtained by RT-qPCR. Non-structural protein 1 release was decreased in pre- and co-treatment but not in post-treatment. Competition assays between the DN59 peptide, envelope protein, and the fragment of domain III "MDKLQLKGMSYSMCTGKF" of the viral envelope of DENV2 and PD1 CD44 showed that our peptide lost its antiviral activity. We demonstrated that our peptide decreased endosome formation, and we propose that it binds to the envelope protein of DENV, inhibiting viral invasion/fusion.

Coupled small molecules target RNA interference and JAK/STAT signaling to reduce Zika virus infection in Aedes aegypti.

Trammell, C., Ramirez, G., Sanchez-Vargas, I., St Clair, L., Ratnayake, O., Luckhart, S., Perera, R., Goodman, A.
04-04-2022
PLoS Pathog
https://doi.org/10.1371/journal.ppat.1010411

The recent global Zika epidemics have revealed the significant threat that mosquito-borne viruses pose. There are currently no effective vaccines or prophylactics to prevent Zika virus (ZIKV) infection. Limiting exposure to infected mosquitoes is the best way to reduce disease incidence. Recent studies have focused on targeting mosquito reproduction and immune responses to reduce transmission. Previous work has evaluated the effect of insulin signaling on antiviral JAK/STAT and RNAi in vector mosquitoes. Specifically, insulin-fed mosquitoes resulted in reduced virus replication in an RNAi-independent, ERK-mediated JAK/STAT-dependent mechanism. In this work, we demonstrate that targeting insulin signaling through the repurposing of small molecule drugs results in the activation of both RNAi and JAK/STAT antiviral pathways. ZIKV-infected Aedes aegypti were fed blood containing demethylasterriquinone B1 (DMAQ-B1), a potent insulin mimetic, in combination with AKT inhibitor VIII. Activation of this coordinated response additively reduced ZIKV levels in Aedes aegypti. This effect included a quantitatively greater reduction in salivary gland ZIKV levels up to 11 d post-bloodmeal ingestion, relative to single pathway activation. Together, our study indicates the potential for field delivery of these small molecules to substantially reduce virus transmission from mosquito to human. As infections like Zika virus are becoming more burdensome and prevalent, understanding how to control this family of viruses in the insect vector is an important issue in public health.

Development of the Sterile Insect Technique to control the dengue vector Aedes aegypti (Linnaeus) in Sri Lanka.

Ranathunge, T., Harishchandra, J., Maiga, H., Bouyer, J., Gunawardena, Y., Hapugoda, M.
04-04-2022
PLoS One
https://doi.org/10.1371/journal.pone.0265244

The Sterile Insect Technique (SIT) is presently being tested to control dengue in several countries. SIT aims to cause the decline of the target insect population through the release of a sufficient number of sterilized male insects. This induces sterility in the female population, as females that mate with sterilized males produce no offspring. Male insects are sterilized through the use of ionizing irradiation. This study aimed to evaluate variable parameters that may affect irradiation in mosquito pupae. An Ae. aegypti colony was maintained under standard laboratory conditions. Male and female Ae. aegypti pupae were separated using a Fay and Morlan glass sorter and exposed to different doses of gamma radiation (40, 50, 60, 70 and 80 Gy) using a Co60 source. The effects of radiation on survival, flight ability and the reproductive capacity of Ae. aegypti were evaluated under laboratory conditions. In addition, mating competitiveness was evaluated for irradiated male Ae. aegypti mosquitoes to be used for future SIT programmes in Sri Lanka. Survival of irradiated pupae was reduced by irradiation in a dose-dependent manner but it was invariably greater than 90% in control, 40, 50, 60, 70 Gy in both male and female Ae. aegypti. Irradiation didn't show any significant adverse effects on flight ability of male and female mosquitoes, which consistently exceeded 90%. A similar number of eggs per female was observed between the non-irradiated groups and the irradiated groups for both irradiated males and females. Egg hatch rates were significantly lower when an irradiation dose above 50 Gy was used as compared to 40 Gy in both males and females. Irradiation at higher doses significantly reduced male and female survival when compared to the non-irradiated Ae. aegypti mosquitoes. Competitiveness index (C) scores of sterile and non-sterile males compared with non-

irradiated male mosquitoes under laboratory and semi-field conditions were 0.56 and 0.51 respectively at 50 Gy. Based on the results obtained from the current study, a 50 Gy dose was selected as the optimal radiation dose for the production of sterile Ae. aegypti males for future SIT-based dengue control programmes aiming at the suppression of Ae. aegypti populations in Sri Lanka.

A retrospective study on the socio-demographic factors and clinical parameters of dengue disease and their effects on the clinical course and recovery of the patients in a tertiary care hospital of Bangladesh.

Prattay, K., Sarkar, M., Shafiullah, A., Islam, M., Raihan, S., Sharmin, N.
04-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010297

Dengue, a mosquito transmitted febrile viral disease, is a serious public health concern in Bangladesh. Despite significant number of incidences and reported deaths each year, there are inadequate number of studies relating the temporal trends of the clinical parameters as well as socio-demographic factors with the clinical course of the disease. Therefore, this study aims to associate the clinical parameters, demographic and behavioral factors of the dengue patients admitted in a tertiary care hospital in Dhaka, Bangladesh during the 2019 outbreak of dengue with the clinical course of the disease. Data were collected from the 336 confirmed dengue in-patients and analyzed using SPSS 26.0 software. Majority of the patients were male (2.2 times higher than female) who required longer time to recover compared to females ($p < 0.01$), urban resident (54.35%) and belonged to the age group of 18-40 years (73.33%). Dengue fever (90.77%) and dengue hemorrhagic fever (5.95%) were reported in most of the dengue patients while fever (98%) was the most frequently observed symptom. A significantly positive association was found between patient's age and number of manifested symptoms ($p = 0.013$). Average duration of stay in the hospital was 4.9 days (SD = 1.652) and patient's recovery time was positively correlated with delayed hospitalization ($p < 0.01$). Additionally, recovery time was negatively correlated with initial blood pressure (both systolic ($p = 0.001$, and diastolic ($p = 0.023$)) and platelet count ($p = 0.003$) of the patients recorded on the first day of hospitalization. Finally, a statistical model was developed which predicted that, hospital stay could be positively associated with an increasing trend of temperature, systolic blood pressure and reduced platelets count. Findings of this study may be beneficial to better understand the clinical course of the disease, identify the potential risk factors and ensure improved patient management during future dengue outbreaks.

Zika virus infection accelerates Alzheimer's disease phenotypes in brain organoids.

Lee, S., Choi, H., Shin, N., Kong, D., Kim, N., Kim, H., Kim, M., Choi, S., Kim, Y., Kang, K.
02-04-2022
Cell Death Discov
https://doi.org/10.1038/s41420-022-00958-x

Alzheimer's disease (AD) is one of the progressive neurodegenerative diseases characterized by β-amyloid (Aβ) production and Phosphorylated-Tau (p-Tau) protein in the cerebral cortex. The precise mechanisms of the cause, responsible for disease pathology and progression, are not well understood because there are multiple risk factors associated with the disease. Viral infection is one of the risk factors for AD, and we demonstrated that Zika virus (ZIKV) infection in brain organoids could trigger AD pathological features, including Aβ and p-Tau expression. AD-related phenotypes in brain organoids were upregulated via endoplasmic reticulum (ER) stress and unfolded protein response (UPR) after ZIKV infection in brain organoids. Under persistent ER stress, activated-double stranded RNA-dependent protein kinase-like ER-resident (PERK) triggered the phosphorylation of Eukaryotic initiation factor 2 (eIF2α) and then BACE, and GSK3α/β related to AD. Furthermore, we demonstrated that pharmacological inhibitors of PERK attenuated Aβ and p-Tau in brain organoids after ZIKV infection.

ZIKV replication is differential in explants and cells of human placental which is suppressed by HSV-2 coinfection.

Torres, L., Capobianco, L., de Souza, A., de Almeida Ribeiro, C., Cascabulho, C., Garzoni, L., Portari, E., Gardel, M., Meuser-Batista, M., de Paula, V., de Souza, E.
28-03-2022
Virology
https://pubmed.ncbi.nlm.nih.gov/35367741

During the Zika fever outbreak in Brazil in 2015-2016, only some babies from infected mothers had teratogenic effects, suggesting that cofactors may influence congenital transmission. We investigated the ZIKV infection profile in explants and isolated cells from full-term human placenta to infection with the Brazilian Zika virus strain ($ZIKV^{BR}$) and the effect of coinfection with the Brazilian Human alphaherpesvirus 2 strain ($HSV\text{-}2^{BR}$) on ZIKV replication. We found that the $ZIKV^{BR}$ infect the explants of amniotic and chorionic membranes, as well as chorionic villi core, but not the trophoblasts layer. It was also observed that ZIKV replication was higher in amniotic cells than chorionic and trophoblasts cells. Upon coinfection, the replication of $ZIKV^{BR}$ was reduced according to exposed $HSV\text{-}2^{BR}$ load in trophoblasts cells and the levels of TNF-α and IL-6 cytokines were also reduced. These findings suggest that the placental cell types and $HSV\text{-}2^{BR}$ coinfection may impact on ZIKV replication.

The calcium channel inhibitor lacidipine inhibits Zika virus replication in neural progenitor cells.

Bezemer, B., van Cleef, K., Overheul, G., Miesen, P., van Rij, R.
30-03-2022
Antiviral Res
https://pubmed.ncbi.nlm.nih.gov/35367280

After decades of being considered non-pathogenic, Zika virus (ZIKV) emerged as an important threat to human health during the epidemic of 2015-2016. ZIKV infections are usually asymptomatic, but can cause Guillain-Barré syndrome in adults and microcephaly in newborns. As there are currently no approved antiviral drugs against ZIKV, we tested anti-ZIKV activity of compounds from the NIH Clinical Collection for which we previously showed antiviral activity against the related dengue virus. One of the top hits from the screen was lacidipine, a 1,4-dihydropyridine calcium antagonist that is approved as an antihypertensive drug. Our data show that lacidipine is antiviral against ZIKV (strain H/PF/2013) in both Vero cells and induced pluripotent stem cell (iPSC)-derived human neural progenitor cells with IC_{50} values of 3.0 µM and <50 nM, respectively. The antiviral effect was also observed against four other ZIKV strains from the African and Asian lineages. Time-of-addition and replicon assays indicated that lacidipine acts at the post-entry stage of the viral replication cycle, inhibiting viral genome replication. Lacidipine altered the subcellular distribution of free cholesterol and neutral lipids, suggesting that the antiviral effect of lacidipine is mediated by altered trafficking of lipids. Together, these results identify lacidipine as a novel inhibitor of ZIKV replication that likely disturbs trafficking of lipids needed for replication organelle formation.

Neutralizing the free radicals could alleviate the disease severity following an infection by positive strand RNA viruses.

Balakrishna Pillai, A., JeanPierre, A., Mariappan, V., Ranganadin, P., S R, R.
03-04-2022
Cell Stress Chaperones
https://doi.org/10.1007/s12192-022-01269-x

Free radical release due to oxidative stress is gaining importance in the field of viral pathogenesis. Recent studies suggest the involvement of oxidative stress and ROS levels in regulating disease virulence during RNA virus infection. Most of the RNA virus infections lead to vascular dysfunction and disease severity. However, the biology of free radicals in maintaining vascular endothelium integrity is not completely understood. In the present review, we discuss some of the common features in positive-strand RNA virus infections such as dengue and SARS-CoV-2 and suggest that anti-oxidant therapy could pave the way to develop therapeutic strategies in combating emerging and re-emerging RNA viruses.

Immunogenicity and safety of booster CYD-TDV dengue vaccine after alternative primary vaccination schedules in healthy individuals aged 9-50 years: a randomised, controlled, phase 2, non-inferiority study.

Coronel-Martinez, D., Park, J., López-Medina, E., Capeding, M., Bonfanti, A., Montalbán, M., Ramírez, I., Gonzales, M., Zambrano, B., Dayan, G., Chen, Z., Wang, H., Bonaparte, M., Rojas, A., Ramírez, J., Verdan, M., Noriega, F.
29-03-2022
Lancet Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35364022

Dengue is endemic in many countries throughout the tropics and subtropics, and the disease causes substantial morbidity and health-care burdens in these regions. We previously compared antibody responses after one-dose, two-dose, or three-dose primary regimens with the only approved dengue vaccine CYD-TDV (Dengvaxia; Sanofi Pasteur, Lyon, France) in individuals aged 9 years and older with previous dengue exposure. In this study, we assessed the need for a CYD-TDV booster after these primary vaccination regimens. In this randomised, controlled, phase 2, non-inferiority study, healthy individuals aged 9-50 years recruited from three sites in Colombia and three sites in the Philippines (excluding those with the usual contraindications to vaccinations) were randomly assigned 1:1:1 via a permuted block method with stratification by site and by age group using an independent voice response system to receive, at 6-month intervals, three doses of CYD-TDV (three-dose group), one dose of placebo followed by two doses of CYD-TDV (two-dose group), or two doses of placebo followed by one dose of CYD-TDV (one-dose group). Participants were also randomly assigned (1:1) to receive a CYD-TDV booster at 1 year or 2 years after the last primary dose. Each CYD-TDV dose was 0·5 mL and administered subcutaneously in the deltoid region of the upper arm. The investigators and sponsor, study staff interacting with the investigators, and participants and their parents or legally acceptable representatives were masked to group assignment. Neutralising antibodies were measured by 50% plaque reduction neutralisation testing, and geometric mean titres (GMTs) were calculated. Due to a change in study protocol, only participants who were dengue seropositive at baseline in the Colombian cohort received a booster vaccination. The primary outcome was to show non-inferiority of the booster dose administered at 1 year or 2 years after the two-dose and three-dose primary regimens; non-inferiority was shown if the lower limit of the two-sided adjusted 95% CI of the between-group (day 28 post-booster dose GMT from the three-dose or two-dose group vs day 28 GMT post-dose three of the three-dose primary regimen [three-dose group]) geometric mean ratio (GMR) was higher than 0·5 for each serotype. Non-inferiority of the 1-year or 2-year booster was shown if all four serotypes achieved non-inferiority. Safety was assessed among all participants who received the booster. This trial is registered with ClinicalTrials.gov, NCT02628444, and is closed to accrual. Between May 2 and Sept 16, 2016, we recruited and enrolled 1050 individuals who received either vaccine or placebo. Of the 350, 348, and 352 individuals

randomly assigned to three-dose, two-dose, and one-dose groups, respectively, 108, 115, and 115 from the Colombian cohort were dengue seropositive at baseline and received a booster; 55 and 53 in the three-dose group received a booster after 1 year and 2 years, respectively, as did 59 and 56 in the two-dose group, and 62 and 53 in the one-dose group. After the three-dose primary schedule, non-inferiority was shown for serotypes 2 (GMR 0·746; 95% CI 0·550-1·010) and 3 (1·040; 0·686-1·570) but not serotypes 1 (0·567; 0·399-0·805) and 4 (0·647; 0·434-0·963) for the 1-year booster, and again for serotypes 2 (0·871; 0·673-1·130) and 3 (1·150; 0·887-1·490) but not serotypes 1 (0·688; 0·479-0·989) and 4 (0·655; 0·471-0·911) for the 2-year booster. Similarly, after the two-dose primary schedule, non-inferiority was shown for serotypes 2 (0·809; 0·505-1·300) and 3 (1·19; 0·732-1·940) but not serotypes 1 (0·627; 0·342-1·150) and 4 (0·499; 0·331-0·754) for the 1-year booster, and for serotype 3 (0·911; 0·573-1·450) but not serotypes 1 (0·889; 0·462-1·710), 2 (0·677; 0·402-1·140), and 4 (0·702; 0·447-1·100) for the 2-year booster. Thus, non-inferiority of the 1-year or 2-year booster was not shown after the three-dose or two-dose primary vaccination regimen in dengue-seropositive participants. No safety concerns occurred with the 1-year or 2-year CYD-TDV booster. CYD-TDV booster 1 year or 2 years after the two-dose or three-dose primary vaccination regimen does not elicit a consistent, meaningful booster effect against all dengue serotypes in participants who are seropositive for dengue at baseline. Sanofi Pasteur. For the Spanish translation of the abstract see Supplementary Materials section.

Dengue vaccines: where are we now and where we are going?

Amorim, J., Birbrair, A.
29-03-2022
Lancet Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35364020

Effects of Guangzhou seasonal climate change on the development of Aedes albopictus and its susceptibility to DENV-2.

Wu, S., He, Y., Wei, Y., Fan, P., Ni, W., Zhong, D., Zhou, G., Zheng, X.
01-04-2022
PLoS One
https://doi.org/10.1371/journal.pone.0266128

The susceptibility of Asian tiger mosquitoes to DENV-2 in different seasons was observed in simulated field environments as a reference to design dengue fever control strategies in Guangzhou. The life table experiments of mosquitoes in four seasons were carried out in the field. The susceptibility of Ae. albopictus to dengue virus was observed in both environments in Guangzhou in summer and winter. Ae. albopictus was infected with dengue virus by oral feeding. On day 7 and 14 after infection, the viral load in the head, ovary, and midgut of the mosquito was detected using real-time fluorescent quantitative PCR. Immune-associated gene expression in infected mosquitoes was performed using quantitative real-time reverse transcriptase PCR. The hatching rate and pupation rate of Ae. albopictus larvae in different seasons differed significantly. The winter hatching rate of larvae was lower than that in summer, and the incubation time was longer than in summer. In the winter field environment, Ae. albopictus still underwent basic growth and development processes. Mosquitoes in the simulated field environment were more susceptible to DENV-2 than those in the simulated laboratory environment. In the midgut, viral RNA levels on day 7 in summer were higher than those on day 7 in winter ($F = 14.459$, $P = 0.01$); ovarian viral RNA levels on day 7 in summer were higher than those on day 7 in winter ($F = 8.656$, $P < 0.001$), but there was no significant difference in the viral load at other time points ($P > 0.05$). Dicer-2 mRNA expression on day 7 in winter was 4.071 times than that on day 7 in summer: the viral load and Dicer-2 expression correlated moderately. Ae. albopictus could still develop and transmit dengue virus in winter in Guangzhou. Mosquitoes under simulated field conditions were more susceptible to DENV-2 than those under simulated laboratory conditions.

Short-term and long-term epidemiological impacts of sustained vector control in various dengue endemic settings: A modelling study.

Sun, H., Koo, J., Dickens, B., Clapham, H., Cook, A.
01-04-2022
PLoS Comput Biol
https://doi.org/10.1371/journal.pcbi.1009979

As the most widespread viral infection transmitted by the Aedes mosquitoes, dengue has been estimated to cause 51 million febrile disease cases globally each year. Although sustained vector control remains key to reducing the burden of dengue, current understanding of the key factors that explain the observed variation in the short- and long-term vector control effectiveness across different transmission settings remains limited. We used a detailed individual-based model to simulate dengue transmission with and without sustained vector control over a 30-year time frame, under different transmission scenarios. Vector control effectiveness was derived for different time windows within the 30-year intervention period. We then used the extreme gradient boosting algorithm to predict the effectiveness of vector control given the simulation parameters, and the resulting machine learning model was interpreted using Shapley Additive Explanations. According to our simulation outputs, dengue transmission would be nearly eliminated during the early stage of sustained and intensive vector control, but over time incidence would gradually bounce back to the pre-intervention level unless the intervention is implemented at a very high level of intensity. The time point at which intervention ceases to be effective is strongly influenced not only by the intensity of vector control, but also by the pre-intervention transmission intensity and the individual-level heterogeneity in biting risk. Moreover, the impact of many transmission model parameters on the intervention

effectiveness is shown to be modified by the intensity of vector control, as well as to vary over time. Our study has identified some of the critical drivers for the difference in the time-varying effectiveness of sustained vector control across different dengue endemic settings, and the insights obtained will be useful to inform future model-based studies that seek to predict the impact of dengue vector control in their local contexts.

Prediction of dengue fever outbreaks using climate variability and Markov chain Monte Carlo techniques in a stochastic susceptible-infected-removed model.

Martheswaran, T., Hamdi, H., Al-Barty, A., Zaid, A., Das, B.
31-03-2022
Sci Rep
https://doi.org/10.1038/s41598-022-09489-y

The recent increase in the global incidence of dengue fever resulted in over 2.7 million cases in Latin America and many cases in Southeast Asia and has warranted the development and application of early warning systems (EWS) for futuristic outbreak prediction. EWS pertaining to dengue outbreaks is imperative; given the fact that dengue is linked to environmental factors owing to its dominance in the tropics. Prediction is an integral part of EWS, which is dependent on several factors, in particular, climate, geography, and environmental factors. In this study, we explore the role of increased susceptibility to a DENV serotype and climate variability in developing novel predictive models by analyzing RT-PCR and DENV-IgM confirmed cases in Singapore and Honduras, which reported high dengue incidence in 2019 and 2020, respectively. A random-sampling-based susceptible-infected-removed (SIR) model was used to obtain estimates of the susceptible fraction for modeling the dengue epidemic, in addition to the Bayesian Markov Chain Monte Carlo (MCMC) technique that was used to fit the model to Singapore and Honduras case report data from 2012 to 2020. Regression techniques were used to implement climate variability in two methods: a climate-based model, based on individual climate variables, and a seasonal model, based on trigonometrically varying transmission rates. The seasonal model accounted for 98.5% and 92.8% of the variance in case count in the 2020 Singapore and 2019 Honduras outbreaks, respectively. The climate model accounted for 75.3% and 68.3% of the variance in Singapore and Honduras outbreaks respectively, besides accounting for 75.4% of the variance in the major 2013 Singapore outbreak, 71.5% of the variance in the 2019 Singapore outbreak, and over 70% of the variance in 2015 and 2016 Honduras outbreaks. The seasonal model accounted for 14.2% and 83.1% of the variance in the 2013 and 2019 Singapore outbreaks, respectively, in addition to 91% and 59.5% of the variance in the 2015 and 2016 Honduras outbreaks, respectively. Autocorrelation lag tests showed that the climate model exhibited better prediction dynamics for Singapore outbreaks during the dry season from May to August and in the rainy season from June to October in Honduras. After incorporation of susceptible fractions, the seasonal model exhibited higher accuracy in predicting outbreaks of higher case magnitude, including those of the 2019-2020 dengue epidemic, in comparison to the climate model, which was more accurate in outbreaks of smaller magnitude. Such modeling studies could be further performed in various outbreaks, such as the ongoing COVID-19 pandemic to understand the outbreak dynamics and predict the occurrence of future outbreaks.

SHAPE-guided RNA structure homology search and motif discovery.

Morandi, E., van Hemert, M., Incarnato, D.
31-03-2022
Nat Commun
https://doi.org/10.1038/s41467-022-29398-y

The rapidly growing popularity of RNA structure probing methods is leading to increasingly large amounts of available RNA structure information. This demands the development of efficient tools for the identification of RNAs sharing regions of structural similarity by direct comparison of their reactivity profiles, hence enabling the discovery of conserved structural features. We here introduce SHAPEwarp, a largely sequence-agnostic SHAPE-guided algorithm for the identification of structurally-similar regions in RNA molecules. Analysis of Dengue, Zika and coronavirus genomes recapitulates known regulatory RNA structures and identifies novel highly-conserved structural elements. This work represents a preliminary step towards the model-free search and identification of shared and conserved RNA structural features within transcriptomes.

Portable sample processing for molecular assays: application to Zika virus diagnostics.

Narahari, T., Dahmer, J., Sklavounos, A., Kim, T., Satkauskas, M., Clotea, I., Ho, M., Lamanna, J., Dixon, C., Rackus, D., Silva, S., Pena, L., Pardee, K., Wheeler, A.
31-03-2022
Lab Chip
https://doi.org/10.1039/d1lc01068a

This paper introduces a digital microfluidic (DMF) platform for portable, automated, and integrated Zika viral RNA extraction and amplification. The platform features reconfigurable DMF cartridges offering a closed, humidified environment for sample processing at elevated temperatures, as well as programmable control instrumentation with a novel thermal cycling unit regulated using a proportional integral derivative (PID) feedback loop. The system operates on 12 V DC power, which can be supplied by rechargeable battery packs for remote testing. The DMF system was optimized for an RNA processing pipeline consisting of the following steps: 1) magnetic-bead based RNA extraction from lysed plasma samples, 2) RNA clean-up, and 3) integrated, isothermal amplification of Zika RNA. The DMF pipeline was coupled to a paper-based, colorimetric cell-free protein expression assay for amplified Zika RNA mediated by toehold switch-based

sensors. Blinded laboratory evaluation of Zika RNA spiked in human plasma yielded a sensitivity and specificity of 100% and 75% respectively. The platform was then transported to Recife, Brazil for evaluation with infectious Zika viruses, which were detected at the 100 PFU mL^{-1} level from a 5 µL sample (equivalent to an RT-qPCR cycle threshold value of 32.0), demonstrating its potential as a sample processing platform for miniaturized diagnostic testing.

Vaginal transmission causes prolonged Zika virus shedding in the vaginal mucosa and delays systemic dissemination.

Balint, E., Somani, A., Giles, E., Feng, E., Vahedi, F., Ashkar, A.
31-03-2022
Immunol Cell Biol
https://doi.org/10.1111/imcb.12549

Zika virus (ZIKV) has emerged as a significant health threat worldwide. Although typically mosquito-borne, recent evidence suggests that ZIKV is also a sexually transmitted virus. While persistent ZIKV infections in male reproductive tissues have been identified, little is understood regarding the outcomes of primary sexual transmission in females. We investigated how the route of infection affects vaginal ZIKV shedding and dissemination. In two mouse models, vaginal infection resulted in prolonged ZIKV shedding in the vaginal mucosa with delayed systemic infection. Furthermore, heightened vaginal inflammation did not influence ZIKV replication or dissemination, in contrast to previous studies of mosquito-borne infection. Thus, vaginal infection significantly alters ZIKV infection kinetics and must be considered when developing novel treatments.

Toxicity of Ulva lactuca and green fabricated silver nanoparticles against mosquito vectors and their impact on the genomic DNA of the dengue vector Aedes aegypti.

Aziz, A.
30-03-2022
IET Nanobiotechnol
https://doi.org/10.1049/nbt2.12082

Marine seaweeds are known to have a potential role against microbial and pesticidal activities. Ulva lactuca, a green macroalgae extract analysed through gas chromatography mass spectrometry reveals 31 compounds. Resistance of mosquito vectors to synthetic insecticides remains a major problem. Discovering and applying natural agents to act against disease vectors is challenging. The activities of the extract and nano-fabricated green synthesised silver nanoparticles were checked for use against Aedes aegypti and Culex pipiens. The crude extract and synthesised silver nanoparticles exhibited a notable larvicidal effect, and very effective inhibition of pupal and adult emergence. Inhibition of adult emergence of Ae.aegypti was 97.7% and in Cu.pipiens, it was 93.3%. Our genotypic study of Deoxyribonucleic acid from treated larvae utilising random primers MA-09, MA-12 and MA-26 revealed damaged nucleotide sequences when compared with the controls. The antimicrobial activity of both the extract and green synthesised nanomaterials showed prominent activity against pathogenic drug resistant bacteria. Our results contribute to further development of eco-friendly insecticides with lower cost of preparation. This could further contribute to further research helping future generations to be free from these deadly disease-causing vectors and pathogenic microbes.

Seasonal variation and intra urban heterogeneity of the entomological risk of transmission of dengue and yellow fever in Abidjan, Côte d'Ivoire.

Guindo-Coulibaly, N., Kpan, M., Adja, A., Kouadio, A., Assouho, K., Zoh, D., Azongnibo, K., Remoue, F., Fournet, F.
30-03-2022
Med Vet Entomol
https://doi.org/10.1111/mve.12571

Dengue and yellow fever are prevalent in Côte d'Ivoire and Aedes (Stegomyia) aegypti (Linnaeus), (Diptera: Culicidae), is known as the main vector. We aimed to assess seasonal variation and spatial heterogeneity in the transmission of both arbovirus diseases in Abidjan. Entomological surveys targeting larvae of A. aegypti, were carried out between November 2015 and August 2016 covering the four climatic seasons including a cohort of 100 houses randomly selected in three neighbourhoods. A. aegypti was the predominant species (96.6%) of mosquitoes resulting from the rearing of harvested larvae, and the only vector of dengue and yellow fever recorded during the study period. The highest proportion of water storage containers (45.5%) which represented the major breeding sites infested by the larvae of A. aegypti, was observed in Anoumabo. The house indices >5% and/or Breteau indices >20 recorded in each neighbourhood, during the different climatic seasons, indicated that there was, a high and permanent, heterogeneity in the transmission risk of dengue and yellow fever between the three neighbourhoods. In terms of transmission risk, Anoumabo was the neighbourhood with the highest risk compared to the two others, then, particular attention should be paid to this site in terms of surveillance by vector control programme in Abidjan.

Infection of human microglial cell line CHME-3 to study neuropathogenesis of chikungunya virus.

Qadri, S., Kumar, N., Santhoshkumar, R., Desai, A., Ravi, V., Venkataswamy, M.
29-03-2022
J Neurovirol
https://doi.org/10.1007/s13365-022-01070-7

Chikungunya virus (CHIKV) infection, generally characterised by fever, rash and debilitating polyarthralgia, and/or arthritis, also causes complications of the central nervous system, including encephalitis. However, the role of microglial cells in the neuropathogenesis of CHIKV is poorly understood. The current study characterised the progression of CHIKV infection

in the human microglial cell line CHME-3. The susceptibility of these cells to CHIKV and the viral replication kinetics were assessed during the early and late phases of infection. The cell viability was determined using the cell viability assay. Ultrastructural changes in CHIKV infected CHME-3 cells were assessed using transmission electron microscopy. The results showed that CHME-3 cells are susceptible to CHIKV infection and support viral replication with no significant loss in cell viability until 72 h post infection. Ultrastructural studies revealed the formation of cytopathic vacuoles-I (CPV-I) in the early stages and CPV-II in later stages with several virions organized along the membrane of CPV-II. Profuse vacuolation was observed in the later stages of infection. Abnormal giant mitochondria with altered cristae were observed in infected cells with an electron-dense matrix. The study establishes CHME-3 cells as a potential model for investigating the role of human microglial cells in neuropathogenicity of CHIKV.

Molecular characterization of chikungunya virus from the first cluster of patients during the 2020 outbreak in Chad.

Yonga, M., Yandai, F., Sadeuh-Mba, S., Abdallah, A., Ouapi, D., Gamougam, K., Abanda, N., Endengue-Zanga, M., Demanou, M., Njouom, R.
29-03-2022
Arch Virol
https://doi.org/10.1007/s00705-022-05427-5

We sequenced a portion of the E1 envelope protein gene of two of four CHIKV RT-PCR-positive samples from the first cluster of chikungunya patients during the 2020 Chad outbreak. Phylogenetic analysis revealed that the viruses belonged to the East/Central/South/African genotype but lacked the E1 A226V and K211E mutations associated with viral adaptability and transmission, suggesting an autochthonous transmission. These sequences are a useful basis for tracking viral evolution in subsequent outbreaks in Chad.

Expanded dengue syndrome presenting with acute liver failure, acute kidney injury, pancreatic involvement, coagulopathy, and multiple intracranial hemorrhages in a young child: a case report.

Thadchanamoorthy, V., Dayasiri, K.
29-03-2022
J Med Case Rep
https://doi.org/10.1186/s13256-022-03348-0

Dengue is a mosquito-borne viral infection that typically occurs in tropical and subtropical countries. The clinical manifestations of dengue infection range from an asymptomatic subclinical course to severe dengue shock syndrome. Besides, dengue can affect any organ in the body and can present with atypical manifestations. We report a 6-year-old previously healthy Tamil child who had dengue complicated with multiorgan involvement. She initially presented with high fever, headache, body aches for 5 days, blood and mucus diarrhea, hematuria, and right knee joint swelling for 2 days. Dengue NS1 antigen was positive on day 2 of febrile illness. She was managed symptomatically in the local hospital for 3 days and transferred to the tertiary care hospital for further management. She was eventually diagnosed as having dengue hemorrhagic fever complicated with multiorgan involvement including acute liver failure, pancreatic involvement, coagulopathy, arthritis, acute kidney injury, and multiple intracranial hemorrhages. The constellation of disease manifestations was identified as expanded dengue syndrome. She was managed with fresh blood, platelet, and cryoprecipitate transfusions and intravenous antibiotics in addition to renal and liver support in the intensive care unit. On day 14 of illness, she deteriorated while on the ventilator and died due to multiple intracranial hemorrhages. The reported child with dengue hemorrhagic fever developed several unusual presentations such as acute liver and renal failure, disseminated intravascular coagulopathy, pancreatic involvement, and multiple intracranial hemorrhages, which form part of expanded dengue syndrome. In the seriously unwell child, it is important to look for unusual complications actively to improve outcomes.

An 8-gene machine learning model improves clinical prediction of severe dengue progression.

Liu, Y., Saul, S., Rao, A., Robinson, M., Agudelo Rojas, O., Sanz, A., Verghese, M., Solis, D., Sibai, M., Huang, C., Sahoo, M., Gelvez, R., Bueno, N., Estupiñan Cardenas, M., Villar Centeno, L., Rojas Garrido, E., Rosso, F., Donato, M., Pinsky, B., Einav, S., Khatri, P.
29-03-2022
Genome Med
https://doi.org/10.1186/s13073-022-01034-w

Each year 3-6 million people develop life-threatening severe dengue (SD). Clinical warning signs for SD manifest late in the disease course and are nonspecific, leading to missed cases and excess hospital burden. Better SD prognostics are urgently needed. We integrated 11 public datasets profiling the blood transcriptome of 365 dengue patients of all ages and from seven countries, encompassing biological, clinical, and technical heterogeneity. We performed an iterative multi-cohort analysis to identify differentially expressed genes (DEGs) between non-severe patients and SD progressors. Using only these DEGs, we trained an XGBoost machine learning model on public data to predict progression to SD. All model parameters were "locked" prior to validation in an independent, prospectively enrolled cohort of 377 dengue patients in Colombia. We measured expression of the DEGs in whole blood samples collected upon presentation, prior to SD progression. We then compared the accuracy of the locked XGBoost model and clinical warning signs in predicting SD. We identified eight SD-associated DEGs in the public datasets and built an 8-gene XGBoost model that accurately predicted SD progression in the independent validation cohort with 86.4% (95% CI 68.2-100) sensitivity and 79.7% (95% CI 75.5-83.9)

specificity. Given the 5.8% proportion of SD cases in this cohort, the 8-gene model had a positive and negative predictive value (PPV and NPV) of 20.9% (95% CI 16.7-25.6) and 99.0% (95% CI 97.7-100.0), respectively. Compared to clinical warning signs at presentation, which had 77.3% (95% CI 58.3-94.1) sensitivity and 39.7% (95% CI 34.7-44.9) specificity, the 8-gene model led to an 80% reduction in the number needed to predict (NNP) from 25.4 to 5.0. Importantly, the 8-gene model accurately predicted subsequent SD in the first three days post-fever onset and up to three days prior to SD progression. The 8-gene XGBoost model, trained on heterogeneous public datasets, accurately predicted progression to SD in a large, independent, prospective cohort, including during the early febrile stage when SD prediction remains clinically difficult. The model has potential to be translated to a point-of-care prognostic assay to reduce dengue morbidity and mortality without overwhelming limited healthcare resources.

Rapid Population-Based Surveillance of Prenatal and Postpartum Experiences During Public Health Emergencies, Puerto Rico, 2016–2018.

Salvesen von Essen, B., D'Angelo, D., Shulman, H., Virella, W., Kortsmit, K., Herrera, B., Díaz, P., Taraporewalla, A., Harrison, L., Warner, L., Vargas Bernal, M.

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Am J Public Health

https://doi.org/10.2105/AJPH.2021.306687

The Pregnancy Risk Assessment Monitoring System-Zika Postpartum Emergency Response study, implemented in Puerto Rico during the Zika virus outbreak (2016-2017) and after Hurricanes Irma and María (2017-2018), collected pregnancy-related data using postpartum hospital-based surveys and telephone follow-up surveys. Response rates of 75% or more were observed across five study surveys. The study informed programs, increased the Puerto Rico Department of Health's capacity to conduct maternal–infant health surveillance, and demonstrated the effectiveness of this methodology for collecting data during public health emergencies. (*Am J Public Health*. 2022;112(4):574-578. https://doi.org/10.2105/AJPH.2021.306687).

Zika Virus after the Public Health Emergency of International Concern Period, Brazil.

Yakob, L.

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Emerg Infect Dis

https://doi.org/10.3201/eid2804.211949

More than 100,000 Zika virus cases have been reported in Brazil since the Public Health Emergency of International Concern period ended in 2016. We analyzed cases in Brazil during 2017-2021 to identify transmission trends and forecast future infection hotspots. Our results can be used for targeted interventions to reduce transmission.

Citywide Integrated Aedes aegypti Mosquito Surveillance as Early Warning System for Arbovirus Transmission, Brazil.

Revue de littérature

Leandro, A., de Castro, W., Lopes, R., Delai, R., Villela, D., de-Freitas, R.

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Emerg Infect Dis

https://doi.org/10.3201/eid2804.211547

Arbovirus epidemiology lacks efficient and timely surveillance systems with accurate outbreak alert signals. We devised a citywide integrated surveillance system combining entomologic, epidemiologic, and entomo-virologic data gathered during 2017-2020 in Foz do Iguaçu, Brazil. We installed 3,476 adult mosquito traps across the city and inspected traps every 2 months. We compared 5 entomologic indices: traditional house and Breteau indices for larval surveys and trap positivity, adult density, and mosquitoes per inhabitant indices for adult trapping. We screened for dengue, Zika, and chikungunya viruses in live adult Aedes aegypti mosquitoes collected from traps. Indices based on adult mosquito sampling had higher outbreak predictive values than larval indices, and we were able to build choropleth maps of infestation levels <36 h after each round of trap inspection. Locating naturally infected vectors provides a timely support tool for local public health managers to prioritize areas for intervention response to prevent virus outbreaks.

Olfactomedin 4 Is a Biomarker for the Severity of Infectious Diseases.

Revue de littérature

Liu, W., Rodgers, G.

08-02-2022

Open Forum Infect Dis

https://doi.org/10.1093/ofid/ofac061

Biomarkers of infectious diseases are essential tools for patient monitoring, diagnostics, and prognostics. Here we review recent advances in our understanding of olfactomedin 4 (OLFM4) in neutrophil biology and of OLFM4 as a new biomarker for certain infectious diseases. OLFM4 is a neutrophil-specific granule protein that is expressed in a subset of human and mouse neutrophils. OLFM4 expression is upregulated in many viral and bacterial infections, as well as in malaria. OLFM4 appears to play an important role in regulating host innate immunity against bacterial infection. Further, higher expression of OLFM4 is associated with severity of disease for dengue virus, respiratory syncytial virus, and malaria infections. In addition, higher expression of OLFM4 or a higher percentage of OLFM4 + neutrophils is associated with poorer outcomes in septic patients. OLFM4 is a promising biomarker and potential therapeutic target in certain infectious diseases.

A novel chimeric dengue vaccine candidate composed of consensus envelope protein domain III fused to C-terminal-modified NS1 protein.

Huang, H., Yang, M., Chen, H., Wang, S., Chang, C., Ho, T., Kao, Y., Tien, S., Lin, H., Chang, P., Lai, Y., Hsiao, Y., Liu, Y., Chao, C., Anderson, R., Yeh, T., Lin, Y., Wan, S.
11-03-2022
Vaccine
https://pubmed.ncbi.nlm.nih.gov/35287985

There is an urgent need for a safe and effective vaccine against dengue virus (DENV) which infects about 390 million humans per year. In the present study we combined modifications of two DENV proteins, the nonstructural protein 1 (NS1) and the envelope (E) protein, to produce a DENV vaccine candidate with enhanced features. One of these modified proteins was a C-terminal-deleted fragment of NS1 called ΔC NS1 which we have shown previously to be protective without the potentially harmful effects of cross-reactive epitopes common to surface antigens on platelets and endothelial cells. The other modified protein was an envelope protein domain III (cEDIII) containing a consensus amino acid sequence among the four serotypes of DENV, which induces neutralizing antibody against all four DENV serotypes. The cEDIII and ΔC NS1 were expressed as a fusion protein cEDIII-ΔC NS1 and its protective effects against DENV were evaluated in a mouse model. C3H/HeN mice were immunized three times with cEDIII-ΔC NS1 fusion protein mixed with alum as adjuvant. Sera collected from cEDIII-ΔC NS1-immunized mice neutralized four serotypes of DENV and also caused complement-mediated cytolysis of HMEC-1 cells infected with each of the four different DENV serotypes. Mice immunized with cEDIII-ΔC NS1 and challenged with DENV showed reduced serum virus titer, soluble NS1 and bleeding time, compared with mice infected with DENV alone. The results reveal that antibodies induced by cEDIII-ΔC NS1 not only show anti-viral efficacy by in vitro assays but also provide protective effects against DENV infection in a mouse model. The cEDIII-ΔC NS1 thus represents a novel, effective DENV vaccine candidate.

Data of knowledge towards Zika Virus infection in Sabah, Malaysia.

Haron, N., Rahim, S., Jani, J., Yusof, N., Amin, Z., Khoo, H., Lee, H., Khor, C., Tan, K., Hassan, M., Wong, C., Agustar, H., Samsusah, A., Hod, R., Bakar, S.
01-03-2022
Data Brief
https://doi.org/10.1016/j.dib.2022.108006

This dataset presents a cross-sectional survey and was conducted to assess the knowledge on Zika Virus infection among adults in Sabah. The data were collected from December 2019 to February 2021, 274 adults living in forest fringe communities were interviewed by trained personnel and have completed the distributed questionnaires. SPSS version 27.0 was used to analyzed the data. These data could serve as auxiliary information and/or research data for other researchers in Sabah. It could also serve as guide or reference data to other researchers outside Sabah who may be interested in carrying out similar research in other state.

Safety and immunogenicity of a single dose, live-attenuated 'tetravalent dengue vaccine' in healthy Indian adults; a randomized, double-blind, placebo controlled phase I/II trial.

Mohanty, L., Prabhu, M., Kumar Mishra, A., Purty, A., Kanungo, R., Ghosh, G., Prahan Kumar, R., Newton Raj, A., Bhushan, S., Kumar Jangir, M., Gupta, A., Bhakri, A.
01-02-2022
Vaccine X
https://doi.org/10.1016/j.jvacx.2022.100142

Dengue fever is the most prevalent mosquito-borne viral disease in the world, with 390 million dengue infections occurring every year. There is an unmet medical need to develop a safe, effective and affordable dengue vaccine against all four Dengue serotype viruses-DENV1, DENV-2, DENV-3 and DENV-4. Panacea Biotec Ltd (PBL) has developed a cell culture-derived, live-attenuated, lyophilized Tetravalent Dengue Vaccine (TDV). Here, in phase I/II study we assessed the safety and immunogenicity of single dose 'Dengue Tetravalent Vaccine' in healthy Indian adults. In the study, 100 healthy adult volunteers aged 18-60 years were enrolled. The participants were allocated to TDV and placebo groups in 3:1 ratio, i.e. 75 participants to TDV group and 25 participants to the placebo group. Enrolled participants were administered a single dose of 0.5 ml of the test vaccine / placebo by subcutaneous route. Primary outcome for safety included all solicited AEs up to 21 days, unsolicited AEs up to 28 days and all AEs/serious adverse events (SAEs) till day 90 post-vaccination. For immunogenicity assessment the primary outcome was seroconversion & seropositivity rate by $PRNT_{50}$ to all four serotype till 90 days. Overall, 100 subjects were vaccinated out of which 8 subjects (5 subjects in vaccine group and 3 subjects in placebo group) dropped out from the study. The most commonly reported solicited local AE was pain and most common solicited systemic AE was headache and fever. No SAE was reported during the study. There was no statistically significant difference between TDV and placebo groups in terms of AEs. Of the 92 subjects who completed all scheduled visits in the study, 59 (81.9%) achieved seroconversion for DENV-1, 56 (77.8%) for DENV-2; 59 (81.9%) for DENV-3 and 57 (79.2%) for DENV-4 in TDV group. The seroconversion rate in the TDV group was statistically significant ($p < 0.001$) compared to placebo.**Clinical trial registration:** CTRI/2017/02/007923.

Dataset for *aedes aegypti* (diptera: Culicidae) and *culex quinquefasciatus* (diptera: Culicidae) collections from key West, Florida, USA, 2010-2020.

Pruszynski, C.
02-02-2022
Data Brief
https://doi.org/10.1016/j.dib.2022.107907

The Florida Keys Mosquito Control District began deploying Biogents® BG Sentinel traps to monitor *Aedes aegypti* (Diptera: Culicidae) populations in Key West during a small autochthonous dengue outbreak that began in November 2009. This paper provides weekly data for twelve collection points from January 2010 through December 2020. BG Sentinel traps were baited with dry ice and proprietary BG Lure and were set in the afternoon and retrieved the following morning totalling 19 collection hours. Trap collections also included *Culex quinquefasciatus* and thus data for that species is also included. The collection data could provide insight into dengue transmission in a small sub-tropical US city.

Pharmacokinetics and Safety of the Nucleoside Analog Antiviral Drug Galidesivir Administered to Healthy Adult Subjects.

Mathis, A., Collins, D., Dobo, S., Walling, D., Sheridan, W., Taylor, R.
19-02-2022
Clin Pharmacol Drug Dev
https://doi.org/10.1002/cpdd.1037

Galidesivir (BCX4430) is an adenosine nucleoside analog broadly active in cell culture against multiple RNA virus families, and active in animal models of viral diseases associated with Ebola, Marburg, yellow fever, Zika, and Rift Valley fever. Current studies demonstrated the pharmacokinetics and safety of the first-in-human evaluations of galidesivir as intramuscular (IM) and intravenous (IV) formulations. Two double-blind, placebo-controlled, dose-ranging studies were conducted enrolling 126 healthy subjects. Study 1 evaluated the safety and tolerability of IM galidesivir over single day dosing, single day dosing ± lidocaine, and 7-day dosing with lidocaine. Study 2 evaluated the safety and tolerability of single ascending doses of IV galidesivir. Safety and tolerability were evaluated via clinical and laboratory monitoring. The plasma concentration-time profile of galidesivir at doses 0.3 to 10 mg/kg IM was characterized by rapid absorption, an initial rapid distribution and clearance phase, and an extended terminal elimination phase. The initial rapid distribution and extended terminal elimination were mimicked in the profile of galidesivir at doses 5 to 20 mg/kg IV. No fatal events or related serious adverse events were reported. No clinically significant dose-related trends in laboratory values, vital signs, electrocardiograms, or echocardiograms were noted. Galidesivir was safe and generally well tolerated.

Mayaro virus infection in French Guiana, a cross sectional study 2003-2019.

Mutricy, R., Matheus, S., Mosnier, É., Martinez-Lorenzi, E., De Laval, F., Nacher, M., Niemetzky, F., Naudion, P., Djossou, F., Rousset, D., Epelboin, L.
10-02-2022
Infect Genet Evol
https://pubmed.ncbi.nlm.nih.gov/35151887

Mayaro Virus is an emerging arbovirus which can be responsible of important outbreaks in tropical regions. A retrospective study was performed in French Guiana, an ultraperipheral region of Europe in Amazonia. We identified 17 human cases between 2003 and 2019. The clinical and biological picture was close to Chikungunya with fever and arthralgia. One patient had acute meningo-encephalitis, and 4 had persistent arthralgia. Physicians should be aware of this virus, as imported cases in Europe have already occurred. AUTHOR SUMMARY: Latin America has experienced several epidemics of arboviruses in recent years, some known for a long time, such as the dengue virus, and others of more recent introduction such as the chikungunya or Zika viruses. There are other arboviruses for the moment more discreet which are rife with low noise in several countries of the continent, such as the Mayaro virus. This alphavirus, with a presentation similar to that of the chikungunya virus, is currently confined to transmission by forest mosquitoes, but its potential to be transmitted by coastal mosquitoes such as Aedes aegypti, make it a potential candidate for a continent-wide epidemic. It therefore seems necessary to know this virus as well as possible in order to anticipate the occurrence of a possible new epidemic. We present here a both demographic and clinical study of this endemic arbovirus disease in French Guiana.

Mannose-binding lectin levels and MBL2 gene polymorphisms are associated with dengue infection in Brazilian children at the early ages.

Sena, M., da Silva Castanha, P., Giles Guimarães, A., Oliveira, P., da Silva, M., Cordeiro, M., Moura, P., Braga, C., Vasconcelos, L.
09-02-2022
Int J Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35150914

The mannose-binding lectin (MBL) plays an important role in innate immunity. Genetically determined variations in serum levels of MBL may influence the susceptibility and clinical outcome of dengue infection in early life. We investigated the MBL2 gene polymorphisms and serum levels of MBL (total and functional) in children with asymptomatic (n=17) and symptomatic (n=29) primary dengue infections and age-matched uninfected children (n=84) enrolled in a birth cohort with dengue in Brazil. Polymorphisms of the MBL2 gene were assessed by reverse transcription-polymerase chain reaction (RT-PCR), whereas the enzyme-linked immunosorbent assay (ELISA) was used to quantify serum levels of MBL. We found that the X allele and YX genotype in the MBL2 were more frequent in the dengue cases than in the control group. Likewise, the LXPA haplotype was exclusively found in dengue cases, thus probably related to dengue infection in our setting. Moreover, we found a higher frequency of the O allele and AO genotype in the control group. Serum levels of total and functional MBL were higher in dengue naïve infants than in dengue cases. MBL2 variants related to lower production of serum MBL were associated with dengue infection in infants, whereas intermediate to high levels of total and functional

serum MBL were associated with protection against dengue infection. These findings highlight the role of MBL2 variants and serum levels of MBL in the susceptibility of children to dengue disease at early ages.

Whole genome analysis identifies intra-serotype recombinants and positive selection sites of dengue virus in mainland China from 2015 to 2020.

Zhu, X., Chen, W., Ma, C., Wang, X., Sun, J., Nie, J., Shi, J., Hu, Y.
01-02-2022
Virus Res
https://pubmed.ncbi.nlm.nih.gov/35121087

Immune pressure can select for escape mutants that can become epidemiologically relevant. Thus, surveillance of recombinants and positively selected mutants of the dengue virus (DENV) are vital for preventing and controlling the dengue fever outbreak. However, little is known about recombinants and positively selected mutants of circulating DENV strains in mainland China. In this study, those variants with recombination and adaptive evolutionary sites of circulating DENV strains were identified during 2015-2020. Phylogenetic analysis showed that the DENV-2 was the dominant epidemic serotype, and the dengue epidemic in China was closely related to the imported virus from Southeast Asian countries. Recombination analysis based on 291 complete genomes of naturally circulating DENV identified 10 new intra-serotype recombinant variants. Two or three recombination regions in a single dengue isolate were also observed. The breakpoints of recombinants were distributed in different regions of the genome. In particular, two recombinant strains (strain DENV-4/China/YN/15DGR394 (2015) and XLLM10666) with extremely large exchange fragments were detected. This large-scale gene fragment exchange (eight genomic regions) of strain DENV-4/China/YN/15DGR394 (2015) with substitutions at both the 5' and 3' ends of the genome, had never been described before. Moreover, selection pressure analyses revealed seven positive selection sites located in regions encoding the NS1, NS3 and NS5 proteins. Overall, this study is the first to report ten specific intra-serotype recombinants and seven positive selection sites of Chinese epidemic strains of DENV, which highlight their significance for DENV surveillance and effective control.

A virus like particle approach to study the Chikungunya virus envelope protein mutations.

Mathew, A., Anukumar, B.
02-02-2022
Virus Genes
https://doi.org/10.1007/s11262-022-01885-w

Virus like particles (VLPs) are used as a tool to study the mutations in the structural genes that influence the virus assembly and entry process. We observed that Chikungunya VLP with the E1:V291I mutation produced more fluorescence-positive cells in Vero cells than the other mutant VLPs (E1:A226V, D284E, and E2:V264A) and wild-type VLP tested in this study. According to the findings, the V291I mutation may aid the virus's ability to enter the cells more efficiently than wild-type VLPs. The study concludes that VLP is a useful model for studying the virus entry process in cells.

Murine models of dengue virus infection for novel drug discovery.

Byrne, A., García, C., Damonte, E., Talarico, L.
31-01-2022
Expert Opin Drug Discov
https://doi.org/10.1080/17460441.2022.2033205

Dengue virus (DENV) is the causative agent of the most prevalent human disease transmitted by mosquitoes in tropical and subtropical regions worldwide. At present, no antiviral drug is available and the difficulties to develop highly protective vaccines against the four DENV serotypes maintain the requirement of effective options for dengue chemotherapy. The availability of animal models that reproduce human disease is a very valuable tool for the preclinical evaluation of potential antivirals. Here, the main murine models of dengue infection are described, including immunocompetent wild-type mice, immunocompromised mice deficient in diverse components of the interferon (IFN) pathway and humanized mice. The main findings in antiviral testing of DENV inhibitory compounds in murine models are also presented. At present, there is no murine model that fully recapitulates human disease. However, immunocompromised mice deficient in IFN-α/β and -γ receptors, with their limitations, have shown to be the most suitable system for antiviral preclinical testing. In fact, the AG129 mouse model allowed the identification of celgosivir, an inhibitor of cellular glucosidases, as a promising option for DENV therapy. However, clinical trials still were not successful, emphasizing the difficulties in the transition from preclinical testing to human treatment.

Comparison of Illumina and Oxford Nanopore Sequencing Technologies for Pathogen Detection from Clinical Matrices Using Molecular Inversion Probes.

Stefan, C., Hall, A., Graham, A., Minogue, T.
25-01-2022
J Mol Diagn
https://pubmed.ncbi.nlm.nih.gov/35085783

Next-generation sequencing is rapidly finding footholds in numerous microbiological fields, including infectious disease diagnostics. Here, we describe a molecular inversion probe panel for the identification of bacterial, viral, and parasitic pathogens. We describe the ability of Illumina and Oxford Nanopore Technologies (ONT) to sequence small amplicons originating from this panel for the identification of pathogens in complex matrices. The panel correctly classified 31 bacterial pathogens directly from positive blood culture bottles with a genus-level concordance of 96.7% and 90.3% on the Illumina

and ONT platforms, respectively. Both sequencing platforms detected 18 viral and parasitic organisms directly from mock clinical samples of plasma and whole blood at concentrations of 10^4 PFU/mL with few exceptions. In general, Illumina sequencing exhibited greater read counts with lower percent mapped reads; however, this resulted in no effect on limits of detection compared with ONT sequencing. Mock clinical evaluation of the probe panel on the Illumina and ONT platforms resulted in positive predictive values of 0.91 and 0.88 and negative predictive values of 1 and 1 from de-identified human chikungunya virus samples compared with gold standard quantitative RT-PCR. Overall, these data show that molecular inversion probes are an adaptable technology capable of pathogen detection from complex sample matrices on current next-generation sequencing platforms.

Molecular identification and phylogeny of Steinernema and Heterorhabditis nematodes and their efficacy in controlling the larvae of Aedes aegypti, a major vector of the dengue virus.

Subkrasae, C., Ardpairin, J., Dumidae, A., Janthu, P., Meesil, W., Muangpat, P., Tandhavanant, S., Thanwisai, A., Vitta, A.
19-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35063414

Aedes aegypti is the mosquito vector of several arboviruses, especially the dengue virus. Aedes aegypti strain resistant to chemical insecticides have been reported worldwide. To tackle this, an entomopathogenic nematode (EPN) may be an alternative bio-control agent. To this end, this study aims to isolate, identify, and analyze the phylogeny of EPNs in Thailand and evaluate their efficacy for controlling the Ae. aegypti larvae. From 12 provinces in Thailand, soil samples were randomly collected, with 118 out of 1,100 them being positive for EPNs (10.73% prevalence) in genera Steinernema (4.46%) and Heterorhabditis (6.27%). Then, molecular discrimination of these two genus was performed based on the sequencing and phylogenetic analysis of the 28S rDNA and internal transcribed spacer regions. The most abundant species of EPN were Heterorhabditis indica, with minor species of Heterorhabditis sp. SGmg3, H. baujardi, S. surkhetense, S. kushidai, S. siamkayai, Steinernema sp. YNd80, Steinernema sp. YNc215, S. guangdongense, and S. huense. The larvicidal activity of five selected EPN isolates were tested against Ae. aegypti. Ten larvae of Ae. aegypti were incubated with different concentration (80, 160, 320, and 640 IJs/larva) of the infective juveniles of EPN in a 24-well and 6-well plates for 4 days. The mortality rates of the larvae were observed daily. Steinernema surkhetense (ePYO8.5_TH) showed the potential to kill mosquito larvae, with the highest mortality rate of 92 ± 9.37% and 89 ± 9.91% after it was treated with 640 IJs/larva in a 24-well plate and 1600 IJs/larva in a 6-well plate, respectively. There is an abundant distribution of EPNs across the country, and S. surkhetense ePYO8.5_TH may be used as a biocontrol agent against Ae. aegypti larvae.

Evaluation of a new NS1 rapid diagnostic test using a single acute-phase serum panel collected during the largest dengue outbreak in Taiwan history in 2015.

Liu, L., Chen, C., Lin, P., Tsai, C., Hsu, M., Huang, B., Tsai, Y., Tsai, J.
21-12-2021
Kaohsiung J Med Sci
https://doi.org/10.1002/kjm2.12490

Dengue virus (DENV) infection results mostly from the bites of virus-carrying Aedes mosquitoes, which results in dengue fever (DF) with or without warning signs, severe dengue, or asymptomatic infections in humans. For point-of care identification of DENV-infected patients, a rapid diagnostic test (RDT) for DENV nonstructural protein 1 (NS1) has been developed to achieve early diagnosis and timely clinical management. We evaluated the performance of a new commercially available dengue NS1 RDT AsiaGen Dengue NS1 Antigen Rapid Diagnosis Test using real-time qRT-PCR as a reference method and compared the results with SD BIOLINE Dengue NS1 Ag using a single acute-phase serum panel collected during the largest dengue outbreak in the history of Taiwan in 2015. The results suggested that the sensitivity and specificity of AsiaGen Dengue NS1 Antigen RDT (96.9% and 100%) were similar to those of SD BIOLINE Dengue NS1 RDT (100% and 100%) for detection in the acute phase of DENV-2 infection. The results suggested that the sensitivity of both RDTs was similar (95.4%~100%) for the sera collected at less than or equal to three days postsymptom onset (PSO). Our results suggested that the two DENV NS1 RDTs used in this study were promising for the timely diagnosis of DENV infection during dengue outbreaks, at least for DENV-2 in areas where authorized medical laboratories are not available or medical resources are limited. However, the performance of AsiaGen DENV NS1 RDTs in the detection of primary/secondary infections and infection by serotypes of DENV other than DENV-2 requires further investigation.

Template requirements of Zika RNA polymerase during in vitro RNA synthesis from the 3'-end of virus minus-strand RNA.

Calmels, C., Métifiot, M., Andreola, M.
13-11-2021
Biochimie
https://pubmed.ncbi.nlm.nih.gov/34780840

As ZIKV continues to spread, many "unknowns" remain and research is needed to advance the understanding of this important pathogen. Viral RNA dependent-RNA polymerases (RdRp) are validated targets for inhibitors of the replication of several viruses. Several studies have set up in vitro enzymatic assays of the RdRp of the Zika virus for testing of candidate inhibitors. While most of these studies use short synthetic polymers, we have shown in a previous work that the Zika polymerase domain is capable of a de novo synthesis of the viral genome using the natural viral RNA as template. Here we have studied the role of the sequences at the 3'end of the

minus-strand RNA in the initiation of the RNA synthesis by the Zika isolated RdRp. Our results strongly suggest that the region containing the 105 first nucleotides from the 3' end of the minus-strand RNA is important for initiation of the positive RNA synthesis. This indicates that this region displays all the primary and secondary structures to be efficiently recognized by the recombinant RdRp in vitro. Moreover, we show that the 46 nucleotides are sufficient to initiate RNA synthesis. In addition, the ZIKV polymerase domain poorly replicated the RNA of other RNA viruses and appeared highly selective for its own RNA.

Infectious disease in an era of global change.

Revue de littérature

Baker, R., Mahmud, A., Miller, I., Rajeev, M., Rasambainarivo, F., Rice, B., Takahashi, S., Tatem, A., Wagner, C., Wang, L., Wesolowski, A., Metcalf, C.
13-10-2021
Nat Rev Microbiol
https://doi.org/10.1038/s41579-021-00639-z

The twenty-first century has witnessed a wave of severe infectious disease outbreaks, not least the COVID-19 pandemic, which has had a devastating impact on lives and livelihoods around the globe. The 2003 severe acute respiratory syndrome coronavirus outbreak, the 2009 swine flu pandemic, the 2012 Middle East respiratory syndrome coronavirus outbreak, the 2013-2016 Ebola virus disease epidemic in West Africa and the 2015 Zika virus disease epidemic all resulted in substantial morbidity and mortality while spreading across borders to infect people in multiple countries. At the same time, the past few decades have ushered in an unprecedented era of technological, demographic and climatic change: airline flights have doubled since 2000, since 2007 more people live in urban areas than rural areas, population numbers continue to climb and climate change presents an escalating threat to society. In this Review, we consider the extent to which these recent global changes have increased the risk of infectious disease outbreaks, even as improved sanitation and access to health care have resulted in considerable progress worldwide.

Discovery of Genes that Modulate Flavivirus Replication in an Interferon-Dependent Manner.

Lesage, S., Chazal, M., Beauclair, G., Batalie, D., Cerboni, S., Couderc, E., Lescure, A., Del Nery, E., Tangy, F., Martin, A., Manel, N., Jouvenet, N.
29-09-2021
J Mol Biol
https://pubmed.ncbi.nlm.nih.gov/34599939

Establishment of the interferon (IFN)-mediated antiviral state provides a crucial initial line of defense against viral infection. Numerous genes that contribute to this antiviral state remain to be identified. Using a loss-of-function strategy, we screened an original library of 1156 siRNAs targeting 386 individual curated human genes in stimulated microglial cells infected with Zika virus (ZIKV), an emerging RNA virus that belongs to the flavivirus genus. The screen recovered twenty-one potential host proteins that modulate ZIKV replication in an IFN-dependent manner, including the previously known IFITM3 and LY6E. Further characterization contributed to delineate the spectrum of action of these genes towards other pathogenic RNA viruses, including Hepatitis C virus and SARS-CoV-2. Our data revealed that APOL3 acts as a proviral factor for ZIKV and several other related and unrelated RNA viruses. In addition, we showed that MTA2, a chromatin remodeling factor, possesses potent flavivirus-specific antiviral functions induced by IFN. Our work identified previously unrecognized genes that modulate the replication of RNA viruses in an IFN-dependent manner, opening new perspectives to target weakness points in the life cycle of these viruses.

Maternal and perinatal outcomes during a Chikungunya outbreak in Kassala, eastern Sudan.

Ali, A., Abdallah, T., Alshareef, S., Al-Nafeesah, A., Adam, I.
27-08-2021
Arch Gynecol Obstet
https://doi.org/10.1007/s00404-021-06204-6

Arboviruses (dengue, Zika, and chikungunya) have recently emerged as an important public health issue and can lead to adverse obstetrics outcomes. The current study was conducted to assess maternal and perinatal outcomes following chikungunya fever/infection and to compare adverse pregnancy outcomes with data from the community collected in a previous study. This study was performed during a chikungunya infection epidemic in Kassala, Sudan by recruiting all pregnant women with a confirmed chikungunya fever diagnosis by using antibodies/detection viral RNA using reverse transcriptase-polymerase chain reaction. Ninety-three pregnant women with confirmed chikungunya infection were enrolled. Their mean (standard deviation) age and parity were 31.6 (3.4) years and 3.5 (1.4), respectively. Of the 93 women, 58 (62.4%) delivered a live infant at term and 18 (19.4%), 13 (13.9%), and 4 (4.3%) women experienced miscarriage, preterm birth, and stillbirth, respectively. In the logistic regression model, severe thrombocytopenia (platelets <50,000 cells/mm^3 (odds ratio [OR]=5.1; confidence interval [CI] 1.8-14; P=0.001) and leukopenia (OR=4.5; CI 2.2-8.8; P<0.001) were predictors for poor obstetric outcomes in pregnant women with chikungunya fever. The rates of miscarriage (18/93 [19.3%] vs. 1/71 [1.4%], P<0.001) and preterm birth (13/93 [13.9%] vs. 2/71 [2.8%], P=0.003) were significantly higher in the current study compared with the rate in the community. Chikungunya infections during pregnancy were associated with miscarriage and preterm birth. Women with severe thrombocytopenia and leukopenia were at higher risk of poor obstetric outcomes. Women with severe thrombocytopenia and leukopenia were at higher risk of poor obstetric outcomes.

Botulinum Toxin Type A in the Spasticity of Cerebral Palsy Related to Congenital Zika Syndrome: An Observational Study.

Armani-Franceschi, G., Luz, C., Lucena, P., d'Afonseca, D., Sales, H., Carvalho, A., Siqueira, I., Silva, K., Portuense, S., Monteiro, L., Bandeira, I., Melo, A., Lucena, R.
13-08-2021
Dev Neurorehabil
https://doi.org/10.1080/17518423.2021.1960917

Investigate the effect of botulinum toxin type-A (BoNT-A) on spasticity and motor performance in children with Cerebral Palsy (CP) related to Congenital Zika Syndrome (CZS). Prospective longitudinal observational study of 34 children with CP referred for BoNT-A treatment. Outcomes were evaluated with a muscle tone assessment scale (Modified Ashworth Scale - MAS) and the Patients' Global Impression of Improvement (PGI-I) scale. Mean age was 32.06 ± 3.07 months and 85% were classified as Gross Motor Function Classification System (GMFCS) V. Primitive reflexes were present in 56% of the sample. The majority of the parents (97.9%) reported improvement in range of motion or reduction in spasticity after treatment with botulinum toxin. No side effects were recorded. When compared to the baseline, median reduction in the MAS was 0.5 (IQR = 0). The findings of this study suggest that BoNT-A may effectively promote functional improvements and reduce muscle tone, improving the child's and family's quality of life.

Chikungunya Fever: Comparison Study of Synovitis and Tenosynovitis of the Hands and Wrists Using Physical Examination, Ultrasound, and MRI Findings.

Leidersnaider, C., Sztajnbok, F., Coutinho, E., Vaz, J., Porangaba, M., Hamdan, P., Martins, P., Constantino, C., Ancillotti, R., Messeder, A., Monteiro, D., Folly, M., Mogami, R.
25-06-2021
J Ultrasound Med
https://doi.org/10.1002/jum.15766

To compare musculoskeletal changes on a physical examination (PE), ultrasound (US) and magnetic resonance imaging (MRI) of the hands and wrists of patients with Chikungunya fever (CF). The sample consisted of 30 patients in the chronic phase of CF. The sites analyzed were the interphalangeal (IP), metacarpophalangeal (MCP) and wrist/mediocarpal (WMC) joints and periarticular soft tissue. The interval between the PE and imaging tests was 7 days, and the interval between US and MRI was 2 days. The kappa coefficient was calculated to estimate the agreement between the PE and US and MRI findings and between the US and MRI findings. Significant agreement was observed between PE and US in the diagnosis of synovitis. The only statistically significant agreement between US and MRI was the finding of flexor tenosynovitis; the agreement was moderate. US has great potential for use in diagnosing synovitis suspected based on a PE. The limited agreement observed between US and MRI, in turn, may suggest a complementary role of these methods.

Chikungunya fever and COVID-19: Oral ulcers are a common feature.

Gueiros, L., Neves, M., Marques, C.
01-12-2020
Oral Dis
https://doi.org/10.1111/odi.13717

Dengue: current state one year before WHO 2010-2020 goals.

Revue de littérature

Wellekens, K., Betrains, A., De Munter, P., Peetermans, W.
22-10-2020
Acta Clin Belg
https://doi.org/10.1080/17843286.2020.1837576

Dengue is a possibly life-threatening human mosquito-borne viral infection widely spread in peridomestic (sub)tropical climates. The global incidence has expanded rapidly in the last decades, with 40% of the world's population currently at risk. To date, no anti-viral treatment other than supportive care exists. In 2015, the first and only dengue-vaccine, CYD-TDV, received marketing authorization. To present the current understanding of dengue in terms of epidemiology, transmission, pathogenesis, disease management and prevention. To illustrate the knowledge gaps that remain to be filled in order to control dengue and achieve the WHO 2010-2020 goals. An updated systematic review (2009-2019) was carried out. The databases Pubmed, Embase and The Cochrane Library were searched along with WHO and CDC guidelines. In total, 39 articles were included. Contemporary climatic and economic factors significantly contributed to the emergence of epidemic dengue. Unfortunately, CYD-TDV failed to meet safety and efficacy demands. New vaccination approaches are in the pipeline along with innovative vector-control strategies. Current anti-viral drug research focuses on repurposing drugs in addition to specific anti-dengue strategies that interfere with viral replication. The lack of understanding dengue pathogenesis and immunology has hampered the development of an effective vaccine. Recent research has provided new insights into the therapeutic and prophylactic approach. Implementation of complementary methods to control disease burden are required considering the socio-economic impact of this rapidly emerging global disease.

Death of guppy fish (*Poecilia reticulata*) leukocytes induced by *in vivo* exposure to temephos and spinosad.

Díaz-Resendiz, K., Hermosillo-Escobedo, A., Ventura-Ramón, G., Toledo-Ibarra, G., Girón-Pérez, D., Bueno-Durán, A., Girón-Pérez, M.
14-07-2020
Int J Environ Health Res
https://doi.org/10.1080/09603123.2020.1791803

Temephos and spinosad are pesticides used for control of

vector-borne diseases such as dengue, chikungunya and zika. However, the inadequate use of these substances has affected the health of non-target organisms. The aim of this study was to evaluate and compare, the effects of temephos and spinosad on leukocyte viability and death, using guppy fish (*Poecilia reticulate)* as a model organism. Guppies were exposed to temephos (10 mg/L) and spinosad (0.5 mg/L) for 7, 14, and 21 days. Afterwards, they were placed in pesticide-free fish tanks (7, 35, and 70 days) for recovery. The results showed that exposure to temephos caused leukocyte death, even at 35 days of recovery. Contrarily, the exposure to spinosad did not cause leukocyte death. This research show, for the first time, that a single dose of temephos causes apoptosis up to 56 days post-exposition, indicating that this pesticide induces chronic effects on immune response cells.

RAGE

Functionalized nanoparticles for brain targeted BDNF gene therapy to rescue Alzheimer's disease pathology in transgenic mouse model.

Arora, S., Kanekiyo, T., Singh, J.
01-04-2022
Int J Biol Macromol
https://pubmed.ncbi.nlm.nih.gov/35378156

Brain-derived neurotrophic factor (BDNF) is actively produced and utilized in cortical circuits throughout life to sustain neuronal function and synaptic plasticity. In animal models of Alzheimer's Disease (AD), highly invasive BDNF gene therapy using viral vectors has successfully shown enhanced synaptic protein expression, proliferation of neurons and attenuation of amyloidogenic processes. However, to eliminate virus-related safety issues and invasive procedures, our present study has explored brain-targeted lipid-based nanoparticles that can deliver plasmid encoding BDNF to brain in a safe and efficient manner. Efficacy of these nanoparticles was tested in early (6-months) and advanced stage (9-months) transgenic APP/PS1 AD mice. Liposomes were surface-functionalized with brain targeting ligand, mannose, and cell-penetrating peptides (rabies virus-derived peptide or penetratin). These bifunctionalized nanoparticles enhanced BDNF expression by ~2 times and resulted in >40% ($p < 0.05$) reduction in toxic amyloid-beta peptides in 6- and 9-months old APP/PS1 mice brains compared to their age-matched untreated controls. Plaque load was reduced ~7 and ~3 times ($p < 0.05$), respectively, whereas synaptic proteins, synaptophysin and PSD-95, were found to be increased >90% ($p < 0.05$) in both age groups of transgenic mice treated with bifunctionalized nanoparticles. No untoward adverse effects were observed throughout treatment, suggesting a safe and effective strategy to rescue AD pathology.

"Using the same hand": The complex local perceptions of integrated one health based interventions in East Africa.

Davis, A., Virhia, J., Bunga, C., Alkara, S., Cleaveland, S., Yoder, J., Kinung'hi, S., Lankester, F.
04-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010298

Neglected Tropical Diseases (NTDs) such as soil transmitted helminths (STH) and human rabies represent a significant burden to health in East Africa. Control and elimination remains extremely challenging, particularly in remote communities. Novel approaches, such as One Health based integrated interventions, are gaining prominence, yet there is more to be learned about the ways in which social determinants affect such programmes. In 2015 a mixed method qualitative study was conducted in northern Tanzania to determine community perceptions towards integrated delivery of two distinct healthcare interventions: treatment of children for STH and dog vaccination for rabies. In order to assess the effectiveness of the integrated approach, villages were randomly allocated to one of three intervention arms: i) Arm A received integrated mass drug administration (MDA) for STH and mass dog rabies vaccination (MDRV); ii) Arm B received MDA only; iii) Arm C received MDRV only. Integrated interventions were looked upon favourably by communities with respondents in all arms stating that they were more likely to either get their dogs vaccinated if child deworming was delivered at the same time and vice versa. Participants appreciated integrated interventions, due to time and cost savings and increased access to essential health care. Analysis of qualitative data allowed deeper exploration of responses, revealing why people appreciated these benefits as well as constraints and barriers to participation in integrated programmes. An interdisciplinary One Health approach that incorporates qualitative social science can provide key insights into complex local perceptions for integrated health service delivery for STH and human rabies. This includes providing insights into how interventions can be improved while acknowledging and addressing critical issues around awareness, participation and underlying health disparities in remote pastoralist communities.

Rabies in the Tropics.

Revue de littérature

Rupprecht, C., Mani, R., Mshelbwala, P., Recuenco, S., Ward, M.
28-03-2022
Curr Trop Med Rep
https://doi.org/10.1007/s40475-022-00257-6

Rabies is an ancient yet still neglected tropical disease (NTD). This review focuses upon highlights of recent research and peer-reviewed communications on the underestimated tropical burden of disease and its management due to the complicated dynamics of virulent viral species, diverse mammalian reservoirs, and tens of millions of exposed humans and animals - and how laboratory-based surveillance

at each level informs upon pathogen spread and risks of transmission, for targeted prevention and control. While both human and rabies animal cases in enzootic areas over the past 5 years were reported to PAHO/WHO and OIE by member countries, still there is a huge gap between these "official" data and the need for enhanced surveillance efforts to meet global program goals. A review of the complex aspects of rabies perpetuation in human, domestic animal, and wildlife communities, coupled with a high fatality rate despite the existence of efficacious biologics (but no therapeutics), warrants the need for a One Health approach toward detection via improved laboratory-based surveillance, with focal management at the viral source. More effective methods to prevent the spread of rabies from enzootic to free zones are needed.

An ELISA-based antigenicity test of rabies recombinant glycoprotein cannot predict its protective potency in vivo.

Volokhov, D., Fry, A., Furtak, V., Jones, R., Musiychuk, K., Norikane, J., Green, B., Srinivas, G., Streatfield, S., Yusibov, V.
29-03-2022
Mol Cell Probes
https://pubmed.ncbi.nlm.nih.gov/35364264

The potency of human and veterinary rabies vaccines is measured based on the National Institute of Health (NIH) potency test that is laborious, time-consuming, variable, and requires sacrifice of large numbers of mice. ELISA-based methods quantifying rabies glycoprotein (rGP) are being developed as potential alternatives to the NIH potency test for release of rabies vaccines. The aim of the current study was focused on the evaluation of in vitro- and in vivo-based assays in order to assess their concurrence for adequate and reliable assessment of immunogenicity and protective potency of a plant-derived recombinant rGP. The recombinant rGP of strain ERA.KK was engineered, expressed and purified from Nicotiana benthamiana plants. The recombinant rGP excluded the transmembrane and intracytoplasmic domains. It was purified by chromatography (≥90%) from the plant biomass, characterized, and mainly presented as high molecular weight forms, most likely soluble aggregates, of the rGP ectodomain. It was well-recognized and quantified by an ELISA, which utilizes two mouse monoclonal antibodies, D1-25 and 1112-1, and which should only recognize the native trimeric form of the rGP. However, in mice, the recombinant rGP did not induce the production of anti-rabies virus neutralizing antibodies and did not confer protection after intracerebral viral challenge. Similar immunogenicity was observed in guinea pigs and rabbits. Our results demonstrate that use of the ELISA method described here is not predictive of performance in vivo. These data highlight the critical need to develop in vitro potency assays that reliably define the antigen content that can induce a protective response.

Spatio-temporal dynamics of rabies and habitat suitability of the common marmoset Callithrix jacchus in Brazil.

Benavides, J., Raghavan, R., Boere, V., Rocha, S., Wada, M., Vargas, A., Voietta, F., de Oliveira E Silva, I., Leal, S., de Castro, A., Arruda, M., Peterson, A., Megid, J., Carrieri, M., Kotait, I.
31-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010254

Rabies transmitted by wildlife is now the main source of human rabies in the Americas. The common marmoset, Callithrix jacchus, is considered a reservoir of rabies causing sporadic and unpredictable human deaths in Brazil, but the extent of the spillover risk to humans remains unknown. In this study, we described the spatiotemporal dynamics of rabies affecting C. jacchus reported to Brazil's Ministry of Health passive surveillance system between 2008 and 2020, and combined ecological niche modelling with C. jacchus occurrence data to predict its suitable habitat. Our results show that 67 outbreaks (91 cases) of rabies affecting C. jacchus were reported by 41 municipalities between January 2008 and October 2020, with a mean of 5 outbreaks/year [range: 1-14]. The maximum number of outbreaks and municipalities reporting cases occurred in 2018, coinciding with higher surveillance of primate deaths due to Yellow Fever. A mean of 3 [1-9] new municipalities reported outbreaks yearly, suggesting potential spatial expansions of the C. jacchus variant in northeastern Brazil and emerging rabies spillover from vampire bat Desmodus rotundus to C. jacchus in the north and south. Outbreaks were concentrated in the states of Ceará (72%) and Pernambuco (16%) up to 2012, but are now reported in Piauí since 2013, in Bahia since 2017 (D. rotundus' antigenic variant, AgV3) and in Rio de Janeiro since 2019 (AgV3). Besides confirming suitable habitat for this primate in the northeast and the east coast of Brazil, our Maximum Entropy model also predicted suitable habitat on the north and the west states of the country but predicted low habitat suitability among inland municipalities of the Caatinga biome reporting rabies. Our findings revealed new areas reporting rabies infecting C. jacchus, highlighting the need to implement strategies limiting spillover to humans and to better understand the drivers of C. jacchus rabies dynamics.

Evidence mapping of current status, impact, prevention and control measures from rabies research in Bangladesh (2010-2021): a scoping review protocol.

Hasan, R., Ferdous, J., Luna, M., Zannat, M.
30-03-2022
BMJ Open
https://doi.org/10.1136/bmjopen-2021-056024

Rabies is one of the priority zoonotic diseases in Bangladesh. Though the rabies cases have been reduced over the years due to the mass dog vaccination programme since 2011 throughout the country, it is still a major health problem in Bangladesh with an annual estimated 200 000 animal bite

cases and over 2000 human deaths. This article presented a scoping review protocol for published literature on rabies in Bangladesh and believes to create impact in Bangladesh by identifying the research gap and guiding the evidence-informed policy adaptation from its findings in the future which will strongly underscore the elimination of Rabies and reduce preventable mortalities. We will attempt to synthesise evidence descriptively on burden and impact of rabies in human population as well as the awareness level and effective control and preventive measures from the available studies on rabies from 2010 to 2021 in Bangladesh. The scoping review is planned following the Joanna Briggs Institute methodology and the major guiding steps are: defining the research questions, determining the eligibility criteria with population, concept and context strategy, stating the plan for evidence searching, selection and data collection, searching for evidence and selection of literature by the inclusion criteria, data collection, descriptive analysis and presentation of the data and reporting of the findings. Search will be conducted for both published and grey literature in English language. Blinded screening processes will be adapted to prevent bias among reviewers. A scoping review synthesises existing knowledge and does not necessitate ethical approval. Results of this scoping review will be submitted to a journal for publication, presented in relevant conferences and disseminated on social media platforms (eg, Twitter) among the global health stakeholders.

Statistical analysis between 2006 and 2019 and forecast of rabies in cattle for 2020 and 2022 in Tocantins State (Brazil), by using the R Studio software.

Santos, A., Ferreira, J., Baptista, F., Alexandrino, B., Silva, M., Gomes, J., Veloso Júnior, J., Tavares, R., Almeida, K.
29-03-2022
Epidemiol Infect
https://doi.org/10.1017/S0950268822000553

Avoidable emergency department visits for rabies vaccination.

Iso, T., Yuan, F., Rizk, E., Tran, A., Saldana, R., Boyareddigari, P., Nguyen, N., Espino, D., Benoit, J., Swan, J.
07-02-2022
Am J Emerg Med
https://pubmed.ncbi.nlm.nih.gov/35183888

Administering subsequent doses of rabies vaccine is not a medical emergency and does not require access to emergency department (ED) services. This study reviewed ED visits for rabies postexposure prophylaxis (PEP) to identify avoidable ED visits for subsequent rabies vaccination. This retrospective study included patients who received human rabies immune globulin (HRIG) or rabies vaccine at 15 EDs of a multi-hospital health system from 2016 to 2018. All ED visits were classified as initial or non-initial healthcare visits after animal exposure. Emergency department visits for non-initial healthcare were classified as necessary (HRIG administration, worsening symptoms, other emergent conditions, or vaccination during a natural disaster) or avoidable (rabies vaccination only). This study included 145 patients with 203 ED visits (113 initial and 90 non-initial healthcare visits). Avoidable ED visits were identified for 19% (28 of 145) of patients and 66% (59 of 90) of ED visits for non-initial healthcare. Contributing factors for avoidable ED visits were suboptimal ED discharge instructions to return to the ED for vaccination (n = 20 visits) and patients' inability to coordinate outpatient follow-up (n = 17 visits). Patients with previous avoidable ED visits had a 73% probability for unnecessarily returning to the ED for vaccination. The average number of avoidable ED visits observed per patient was 0.41 (95% CI = 0.25 to 0.56). Since the Centers for Disease Control and Prevention reports that 30,000 to 60,000 Americans initiates rabies PEP each year, we estimate that 7500 to 33,600 avoidable ED visits occur for rabies vaccination in the US each year. One of 5 patients who received rabies PEP in the ED had avoidable ED visits for subsequent rabies vaccination. This study highlights systemic lack of coordination following ED discharge and barriers to accessing rabies vaccine.

Tylvalosin demonstrates anti-parasitic activity and protects mice from acute toxoplasmosis.

Yuan, W., Jia, H., Tang, X., Xin, T., Liu, X., Wang, Z., Li, X., Zhao, Z., Liu, L., Liang, L., Zhao, X., Zhao, Z.
03-02-2022
Life Sci
https://pubmed.ncbi.nlm.nih.gov/35123999

Toxoplasmosis, caused by Toxoplasma gondii (Tg), is one of the most prevalent zoonotic diseases worldwide. Currently, safe and efficient therapeutic options for this disease are still being developed, and are urgently needed. Tylvalosin (Tyl), a broad-spectrum third-generation macrolide, exhibits anti-bacterial, anti-viral, and anti-inflammatory properties. The present study aims to explore the anti-parasitic and immunomodulation activities of Tyl against Tg, and the underlying mechanism. Adhesion, invasion, replication, proliferation, plaque, reversibility, immunofluorescence assays and transmission electron microscopy were utilized to determine the anti-Toxoplasma effect of Tyl. With acute toxoplasmosis model and rabies virus-induced brain inflammation model, the anti-toxoplasmosis and immunomodulation activities of Tyl were assessed by colorimetric assay, histopathological and Oil red O staining, and real-time quantitative PCR. The involved molecular mechanisms were investigated by western blotting and immunohistochemical staining. Tyl (5 and 10 μg/ml) can inhibit Tg propagation, and damage its ultrastructure irreversibly. The combination of Tyl and Pyrimethamine (Pyr) exhibits a better synergistic effect. Tyl (50 and 100 mg/kg) treatment intraperitoneally can delay mice death and improve survival rate, accompanying the reduced histopathological score and parasite load in the indicated tissues, espically for ileum, liver, spleen, lung and brain. Furthermore, Tg can modulate host phospho-p38 MAPK (pp38), subtilisin/kexin-

isozyme-1 (SKI-1)-sterol regulatory element binding protein-1 (SREBP-1) (SKI-1-SREBP-1) pathway and peroxisome proliferators-activated receptor δ (PPARδ), while Tyl is able to reverse these signal pathways close to normal levels. Our findings indicate that Tyl exhibits anti-Toxoplasma activity and protects mice from acute toxoplasmosis.

A multisynaptic pathway from the ventral midbrain toward spinal motoneurons in monkeys.

Suzuki, M., Inoue, K., Nakagawa, H., Ishida, H., Kobayashi, K., Isa, T., Takada, M., Nishimura, Y.
17-02-2022
J Physiol
https://doi.org/10.1113/JP282429

Motivation boosts motor performance. Activity of the ventral midbrain (VM), consisting of the ventral tegmental area (VTA), the substantia nigra pars compacta (SNc) and the retrorubral field (RRF), plays an important role in processing motivation. However, little is known about the neural substrate bridging the VM and the spinal motor output. We hypothesized that the VM might exert a modulatory influence over the descending motor pathways. By retrograde transneuronal labelling with rabies virus, we demonstrated the existence of multisynaptic projections from the VM to the cervical enlargement in monkeys. The distribution pattern of spinal projection neurons in the VM exhibited a caudorostral gradient, in that the RRF and the caudal part of the SNc contained more retrogradely labelled neurons than the VTA and the rostral part of the SNc. Electrical stimulation of the VM induced muscle responses in the contralateral forelimb with a delay of a few milliseconds following the responses of the ipsilateral primary motor cortex (M1). The magnitude and number of evoked muscle responses were associated with the stimulus intensity and number of pulses. The muscle responses were diminished during M1 inactivation. Thus, the present study has identified a multisynaptic VM-spinal pathway that is mediated, at least in part, by the M1 and might play a pivotal role in modulatory control of the spinal motor output. KEY POINTS: Motivation to obtain reward is thought to boost motor performance, and activity in the ventral midbrain is important to the motivational process. Little is known about a neural substrate bridging the ventral midbrain and the spinal motor output. Retrograde trans-synaptic experiments revealed that the ventral midbrain projects multisynaptically to the spinal cord in macaque monkeys. Ventral midbrain activation by electrical stimulation generated cortical activity in the motor cortex and forelimb muscle activity. A multisynaptic ventral midbrain-spinal pathway most probably plays a pivotal role in modulatory control of the spinal motor output.

Time to drink: Activating lateral hypothalamic area neurotensin neurons promotes intake of fluid over food in a time-dependent manner.

Kurt, G., Kodur, N., Quiles, C., Reynolds, C., Eagle, A., Mayer, T., Brown, J., Makela, A., Bugescu, R., Seo, H., Carroll, Q., Daniels, D., Robison, A., Mazei-Robison, M., Leinninger, G.
19-01-2022
Physiol Behav
https://pubmed.ncbi.nlm.nih.gov/35063424

The lateral hypothalamic area (LHA) is essential for ingestive behavior but has primarily been studied in modulating feeding, with comparatively scant attention on drinking. This is partly because most LHA neurons simultaneously promote feeding and drinking, suggesting that ingestive behaviors track together. A notable exception are LHA neurons expressing neurotensin (LHA^{Nts} neurons): activating these neurons promotes water intake but modestly restrains feeding. Here we investigated the connectivity of LHA^{Nts} neurons, their necessity and sufficiency for drinking and feeding, and how timing and resource availability influence their modulation of these behaviors. LHA^{Nts} neurons project broadly throughout the brain, including to the lateral preoptic area (LPO), a brain region implicated in modulating drinking behavior. LHA^{Nts} neurons also receive inputs from brain regions implicated in sensing hydration and energy status. While activation of LHA^{Nts} neurons is not required to maintain homeostatic water or food intake, it selectively promotes drinking during the light cycle, when ingestive drive is low. Activating LHA^{Nts} neurons during this period also increases willingness to work for water or palatable fluids, regardless of their caloric content. By contrast, LHA^{Nts} neuronal activation during the dark cycle does not promote drinking, but suppresses feeding during this time. Finally, we demonstrate that the activation of the $LHA^{Nts} \rightarrow$ LPO projection is sufficient to mediate drinking behavior, but does not suppress feeding as observed after generally activating all LHA^{Nts} neurons. Overall, our work suggests how and when LHA^{Nts} neurons oppositely modulate ingestive behaviors.

What can we learn from over a decade of testing bats in New South Wales to exclude infection with Australian bat lyssaviruses?

Revue de littérature

O'Connor, T., Finlaison, D., Kirkland, P.
18-01-2022
Aust Vet J
https://doi.org/10.1111/avj.13143

Australian Bat lyssaviruses (ABLV) are known to be endemic in bats in New South Wales (NSW), Australia. These viruses pose a public health risk because they cause a fatal disease in humans that is indistinguishable from classical rabies infection. All potentially infectious contact between bats and humans, or between bats and domestic animals, should be investigated to assess the risk of virus transmission by submitting the bat for testing to exclude ABLV infection. The aim of this study was to establish the prevalence of ABLV infection in bats submitted for testing in NSW and to document any trends or changes in submission and bat details. We examined all submissions of samples for ABLV testing received by the NSW Department of Primary Industries Virology Laboratory for the 13-year period between 1 May

2008 and 30 April 2021. Fifty-four (4.9%) ABLV-infected bats were detected, with some clustering of positive results. This is greater than the prevalence estimated from wild-caught bats. All bats should be considered a potential source of ABLV. In particular, flying-foxes with rabies-like clinical signs, and with known or possible human interaction, pose the highest public health risk because they are more likely to return a positive result for ABLV infection. This review of ABLV cases in NSW will help veterinarians to recognise the clinical presentations of ABLV infection in bats and emphasises the importance of adequate rabies vaccination for veterinarians.

Community Engagement in the Diagnosis and Control of a Bovine Paralytic Rabies Outbreak in Two Rural Communities of Mexico.

Galarde-López, M., Quiroz-Rocha, G., Candanosa-Aranda, I., Soberanis-Ramos, O., García-García, L.
12-09-2021
J Agromedicine
https://doi.org/10.1080/1059924X.2021.1979153

Rabies is a neglected zoonosis with adverse public health effects. We describe the community engagement in containing a bovine paralytic rabies outbreak in two rural communities of Mexico. We carried out a participatory rapid appraisal using different community participation techniques for 2 weeks, including information sharing, community meetings, prioritization of activities, and training. In addition to the animal census and vaccination, necropsy and immunofluorescence tests were performed to diagnose rabies. Cattle mortality during the outbreak of bovine paralytic rabies was 4.5% (15/331); 1446 anti-rebies vacines were applied, directly benefiting 94 families. Members of two rural communities were trained. The continuous exchange of information among the stakeholders allowed us to inform, consult, involve, and empower community members. Community participation played an essential role in identifying a common problem, implementing activities to contain it, and successfully safeguarding public health, animal production, and food security.

TRACHOME

Prevalence of Trachoma following Implementation of the SAFE Strategy in Three Local Government Areas of Taraba State, North Eastern Nigeria.

Olamiju, F., Isiyaku, S., Olobio, N., Mogaji, H., Achu, I., Muhammad, N., Boyd, S., Bakhtiari, A., Ebenezer, A., Jimenez, C., Solomon, A., Harding-Esch, E., Mpyet, C.
30-03-2022
Ophthalmic Epidemiol
https://doi.org/10.1080/09286586.2022.2045025

In 2019-2020, one round of antibiotic mass drug administration (MDA) was implemented for trachoma elimination purposes in Donga, Gashaka, and Ussa local government areas (LGAs) of Taraba State, Nigeria, following baseline surveys in 2009 (Donga and Gashaka) and 2013-2014 (Ussa). Here, trachoma prevalence post-MDA in these three LGAs is reported. In 2019 (Gashaka and Ussa) and 2020 (Donga), population-based, cross-sectional surveys were conducted following World Health Organization (WHO) guidance. A two-stage cluster sampling strategy was used. All residents of selected households aged ≥1 year were examined by Tropical Data-certified graders for trachomatous inflammation-follicular (TF) and trachomatous trichiasis (TT) using the WHO simplified trachoma grading scheme. Data on water, sanitation, and hygiene (WASH) access were also collected. A total of 1,883 households participated. From these households, 4,885 children aged 1-9 years were enumerated, and 4,866 (99.6%) examined. There were 5,050 eligible adults (aged ≥15 years) enumerated in the same households, of whom 4,888 (96.8%) were examined. Age-adjusted TF prevalence in children aged 1-9 years was 0.22% (95% CI: 0.00-0.65) in Donga, 0.0% in Gashaka, and 0.19% (95% CI: 0.00-0.44) in Ussa. The age- and gender-adjusted TT prevalence unknown to the health system in adults aged ≥15 years was 0.08% (95% CI: 0.00-0.19) in Donga, 0.02% (95% CI: 0.00-0.06) in Gashaka, and 0.10% (95% CI: 0.01-0.18) in Ussa. In Donga, Gashaka, and Ussa, respectively, 66%, 49% and 63% of households had access to an improved drinking water source, and 68%, 56% and 29% had access to an improved latrine. In all LGAs, the elimination thresholds for TF and TT unknown to the health system have been attained in the target age groups. These LGAs should be re-surveyed after 2 years to show that reductions in TF prevalence have been sustained in the absence of MDA. Health authorities should continue to improve WASH facilities to reduce the risk of later recrudescence.

Distichiasis: An update on etiology, treatment and outcomes.

Revue de littérature

Singh, S.
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Indian J Ophthalmol
https://doi.org/10.4103/ijo.IJO_1141_21

Distichiasis, an extra row of eyelashes emerging from meibomian gland orifices, occurs due to the metaplastic transition of sebaceous glands into the pilosebaceous unit. It can present congenitally, such as in lymphedema distichiasis syndrome, or secondary to acquired conditions, such as cicatrizing conjunctivitis, trachoma. This review summarizes the etiology of distichiasis, its presentation, the evolution of various surgical techniques, and their outcomes in human and animal eyes. The published literature has focused on the different treatment modalities and their outcomes; the etiopathogenesis of this condition remains elusive. Truncating mutations (missense, frameshift, and nonsense) in the Forkhead family gene FOXC2 are involved in the distichiasis-

lymphedema syndrome. The treatment options are no different for congenital versus acquired distichiasis, with no specific available algorithms. Acquired distichiasis in cicatrizing ocular surface diseases is difficult to manage, and existing treatment options offer success rates of 50%-60%. The outcomes of electroepilation or direct cryotherapy are not as good as surgical excision of distichiatic lashes after splitting the anterior and posterior lamella under direct visualization. The marginal tarsectomy with or without free tarsoconjunctival graft has shown good results in eyes with congenital and acquired distichiasis. The details of differences between normal and distichiatic lash, depth, or course of distichiatic eyelashes remain largely unknown. Studies exploring the distichiatic eyelash depth might improve the outcomes of blind procedures such as cryotherapy or radiofrequency-assisted epilation.

Global progress toward the elimination of active trachoma: an analysis of 38 countries.

Renneker, K., Abdala, M., Addy, J., Al-Khatib, T., Amer, K., Badiane, M., Batcho, W., Bella, L., Bougouma, C., Bucumi, V., Chisenga, T., Dat, T., Dézoumbé, D., Elshafie, B., Garae, M., Goepogui, A., Hammou, J., Kabona, G., Kadri, B., Kalua, K., Kanyi, S., Khan, A., Marfo, B., Matendechero, S., Meite, A., Minnih, A., Mugume, F., Olobio, N., Omar, F., Phiri, I., Sanha, S., Sharma, S., Seife, F., Sokana, O., Taoaba, R., Tesfazion, A., Traoré, L., Uvon, N., Yaya, G., Logora, M., Hooper, P., Emerson, P., Ngondi, J.

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Lancet Glob Health

https://pubmed.ncbi.nlm.nih.gov/35303459

Global elimination of trachoma as a public health problem was targeted for 2020. We reviewed progress towards the elimination of active trachoma by country and geographical group. In this retrospective analysis of national survey and implementation data, all countries ever known to be endemic for trachoma that had either implemented at least one trachoma impact survey shown in the publicly available Trachoma Atlas, or are in Africa were invited to participate in this study. Scale-up was described according to the number of known endemic implementation units and mass drug administration implementation over time. The prevalence of active trachoma-follicular among children aged 1-9 years (TF_{1-9}) from baseline, impact, and surveillance surveys was categorised and used to show programme progress towards reaching the elimination threshold (TF_{1-9} <5%) using dot maps, spaghetti plots, and boxplots. We included data until Nov 10, 2021, for 38 countries, representing 2097 ever-endemic implementation units. Of these, 1923 (91·7%) have had mass drug administration. Of 1731 implementation units with a trachoma impact survey, the prevalence of TF_{1-9} had reduced by at least 50% in 1465 (84·6%) implementation units and 1182 (56·4%) of 2097 ever-endemic implementation units had reached the elimination threshold. 2 years after reaching a TF_{1-9} prevalence below 5%, most implementation units sustained this target; however, 58 (56·3%) of 103 implementation units in Ethiopia showed recrudescence. Global elimination of trachoma as a public health problem by 2020 was not possible, but this finding masks the great progress achieved. Implementation units in high baseline categories and recrudescent TF_{1-9} might prolong the attainment of elimination of active trachoma. Elimination is delayed but, with an understanding of the patterns and timelines to reaching elimination targets and a commitment toward meeting future targets, global elimination can still be achieved by 2030. None.

Trachoma control using water, sanitation, and hygiene - Authors' reply.

Aragie, S., Lietman, T., Keenan, J.

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Lancet Glob Health

https://pubmed.ncbi.nlm.nih.gov/35303456

Trachoma control using water, sanitation, and hygiene.

Taylor, H.

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Lancet Glob Health

https://pubmed.ncbi.nlm.nih.gov/35303455

The roles of mouse double minute 2 (MDM2) oncoprotein in ocular diseases: A review.

Revue de littérature

Jiang, H., Luo, J., Lei, H.

05-01-2022

Exp Eye Res

https://pubmed.ncbi.nlm.nih.gov/34998788

Mouse double minute 2 (MDM2), an E3 ubiquitin ligase and the primary negative regulator of the tumor suppressor p53, cooperates with its structural homolog MDM4/MDMX to control intracellular p53 level. In turn, overexpression of p53 upregulates and forms an autoregulatory feedback loop with MDM2. The MDM2-p53 axis plays a pivotal role in modulating cell cycle control and apoptosis. MDM2 itself is regulated by the PI3K-AKT and RB-E2F-ARF pathways. While amplification of the MDM2 gene or overexpression of MDM2 (due to MDM2 SNP T309G, for instance) is associated with various malignancies, numerous studies have shown that MDM2/p53 alterations may also play a part in the pathogenetic process of certain ocular disorders. These include cancers (retinoblastoma, uveal melanoma), fibrocellular proliferative diseases (proliferative vitreoretinopathy, pterygium), neovascular diseases, degenerative diseases (cataract, primary open-angle glaucoma, age-related macular degeneration) and infectious/inflammatory diseases (trachoma, uveitis). In addition, MDM2 is implicated in retinogenesis and regeneration after optic nerve injury. Anti-MDM2 therapy has shown potential as a novel approach to treating these diseases. Despite major safety concerns, there are high

expectations for the clinical value of reformative MDM2 inhibitors. This review summarizes important findings about the role of MDM2 in ocular pathologies and provides an overview of recent advances in treating these diseases with anti-MDM2 therapies.

Discord between presence of follicular conjunctivitis and Chlamydia trachomatis infection in a single Torres Strait Island community: a cross-sectional survey.

Lynch, K., Brian, G., Ahwang, T., Newie, T., Newie, V., Perrett, C., Wharton, G., Brown, A., Tozer, S., Kaldor, J., Whop, L., Andrews, R., Lambert, S.
03-01-2022
Aust N Z J Public Health
https://doi.org/10.1111/1753-6405.13179

Recent surveys identified trachomatous inflammation - follicular (TF) at endemic levels in the Torres Strait Islands; however, local health staff do not report trachomatous trichiasis (TT) in adults. We undertook a cross-sectional survey involving eye examination and microbiological testing to better understand this disconnect. We examined 169 of 207 (82%) residents and collected ocular swabs for polymerase chain reaction (PCR) testing for Chlamydia trachomatis. Other viral PCR tests and bacterial culture were also performed. TF prevalence in children aged 5-9 years was 23% (7/30). No ocular C. trachomatis was identified by PCR. For the 72 participants (43%) with follicles, bacterial culture was positive for 11 (15%) individuals. No individual had trachomatous trichiasis. Follicular conjunctivitis consistent with TF was prevalent but ocular C. trachomatis and cicatricial trachoma were absent. Non-chlamydial infections or environmental causes of follicular conjunctivitis may be causing TF in this community. In similar settings, reliance on simplified clinical assessment alone may lead to an overestimation of the public health problem posed by trachoma. Consideration should be given to incorporating C. trachomatis PCR, and in certain settings, a detailed clinical exam could be performed by an experienced ophthalmologist during prevalence surveys.

ULCERE DE BURULI

Mycobacterial skin infection.

Gardini, G., Gregori, N., Matteelli, A., Castelli, F.
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Curr Opin Infect Dis
https://doi.org/10.1097/QCO.0000000000000820

The aim of this article is to review the most recent evidences concerning mycobacterial skin infections, limiting the period of literature research to 2020--2021. Mycobacterial skin infections include a heterogeneous group of cutaneous diseases.Cutaneous tuberculosis is usually the result of hematogenous dissemination or spread from underlying foci and it must be distinguished from tuberculids, resulting from the immunological reaction to Mycobacterium tuberculosis antigens. Leprosy prevalence was drastically reduced after introduction of multidrug therapy in the 1980s, but cases are still reported due to underdiagnosis, and animal and environmental reservoirs. Recent advances concentrate in the diagnostic field. Specific guidelines for the treatment of nontuberculous mycobacteria skin infections are missing and surgical procedures may be required. Prognosis is better as compared to nontuberculous mycobacteria lung disease. Rapid laboratory-confirmed diagnosis of Buruli ulcer may be achieved by the IS2404 PCR. Among new drugs, telacebec is promising in terms of potency, shorter duration and tolerability in animal studies. A clinical trial in humans is planned. Mycobacterial cutaneous lesions are nonpathognomonic and clinical suspicion must be confirmed by culture or molecular detection. Long-course multidrug treatment is required based on susceptibility tests. Surgical intervention may also be required. Rehabilitation and psychosocial support reduce long-term physical and mental consequences mostly in Buruli ulcer and leprosy.

The search for a Buruli Ulcer vaccine and the effectiveness of the Bacillus Calmette-Guérin vaccine.

Revue de littérature

Ishwarlall, T., Okpeku, M., Adeniyi, A., Adeleke, M.
20-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35065013

Buruli Ulcer is a neglected tropical disease that is caused by Mycobacterium ulcerans. It is not fatal; however, it manifests a range of devastating symptoms on the hosts' bodies. Various drugs and treatments are available for the disease; however, they are often costly and have adverse effects. There is still much uncertainty regarding the mode of transmission, vectors, and reservoir. At present, there are no official vector control methods, prevention methods, or a vaccine licensed to prevent infection. The Bacillus Calmette-Guérin vaccine developed against tuberculosis has some effectiveness against M. ulcerans. However, it is unable to induce long-lasting protection. Various types of vaccines have been developed based specifically against M. ulcerans; however, to date, none has entered clinical trials or has been released for public use. Additional awareness and funding are needed for research in this field and the development of more treatments, diagnostic tools, and vaccines.

PIAN

LAMP4yaws: *Treponema pallidum*, *Haemophilus ducreyi* loop mediated isothermal amplification - protocol for a cross-sectional, observational, diagnostic accuracy study.

Handley, B., González-Beiras, C., Tchatchouang, S., Basing, L., Hugues, K., Bakheit, M., Becherer, L., Ries, C., Njih Tabah, E., Crucitti, T., Borst, N., Lüert, S., Frischmann, S., Haerpfer, T., Landmann, E., Amanor, I., Sylla, A., Kouamé-Sina, M., Ndzomo-Ngono, J., Tano, A., Arhinful, D., Awondo, P., Ngazoa Kakou, S., Eyangoh, S., Addo, K., Harding-Esch, E., Knauf, S., Mitjà, O., Marks, M.
29-03-2022
BMJ Open
https://doi.org/10.1136/bmjopen-2021-058605

Yaws, caused by the bacterium *Treponema pallidum* subsp. *pertenue,* is a neglected tropical disease targeted for eradication by 2030. Improved diagnostics will be essential to meet this goal. Diagnosis of yaws has relied heavily on clinical and serological tools. However, the presence of coendemic cutaneous skin ulcer diseases, such as lesions caused by *Haemophilus ducreyi* (*HD*), means these techniques do not provide a reliable diagnosis. Thus, new diagnostic tools are needed. Molecular tools such as PCR are ideal, but often expensive as they require trained technicians and laboratory facilities, which are often not available to national yaws programmes. The LAMP4yaws project is a cross-sectional, observational, diagnostic accuracy study of a combined *Treponema pallidum* (*TP*) and *HD* loop mediated isothermal amplification (TPHD-LAMP) test performed under real world conditions in three endemic countries in West Africa. Individuals with serologically confirmed yaws will be recruited in Cameroon, Côte d'Ivoire and Ghana. Each participant will provide paired swabs, one of which will be sent to the respective national reference laboratory for yaws quantitative PCR and the other will be tested for both *TP* and *HD* using the TPHD-LAMP test at local district laboratories. Sensitivity and specificity of the TPHD-LAMP test will be calculated against the reference standard qPCR. We will also assess the acceptability, feasibility and cost-effectiveness of the test. We anticipate that results from this study will support the adoption of the TPHD-LAMP test for use in global yaws eradication efforts. We have received ethical approval from all relevant institutional and national ethical committees. All participants, or their parents or guardians, must provide written informed consent prior to study enrolment. Study results will be published in an open access journal and disseminated with partners and the World Health Organization. NCT04753788.

LEPRE

Leprosy: clinical and immunopathological characteristics.

Revue de littérature

Froes, L., Sotto, M., Trindade, M.
01-04-2022
An Bras Dermatol
https://pubmed.ncbi.nlm.nih.gov/35379512

Leprosy, a disease caused by Mycobacterium leprae, has polymorphic neurocutaneous manifestations strongly correlated with the host immune response. Peripheral neural damage can lead to sensory and motor losses, as well as deformities of the hands and feet. Both innate and acquired immune responses are involved, but the disease has been classically described along a Th1/Th2 spectrum, where the Th1 pole corresponds to the more limited presentations and the Th2 to the multibacillary ones. The aim of this review is to discuss this dichotomy in light of the current knowledge of the cytokines, T helper subpopulations, and regulatory T cells involved in each presentation of leprosy. The text will also address leprosy reactions related to increased inflammatory activity in both limited and multibacillary presentations, leading to exacerbation of chronic signs and symptoms and/or the development of new ones. Despite the efforts of many research groups around the world, there is no standardized serological test/biological marker for diagnosis so far, even in endemic areas, which could contribute to the eradication of leprosy.

How do Americans perceive the stigma of leprosy?

Corrigan, P., Nieweglowski, K., Morris, S.
03-04-2022
Psychol Health Med
https://doi.org/10.1080/13548506.2022.2061718

The stigma of leprosy will have reduced effects if people cannot reliably perceive it. Two factors impact these perceptions: familiarity and entitativity. One hundred and forty-five participants tested this assertion using an online platform to complete measures of stigma about leprosy as well as measures of familiarity and entitativity. The group of 145 completed the same measures of stigma, entitativity, and familiarity 1 week later. Standard deviations of time 1 and time 2 measures of stigma were used as indices of consistent (reliable) perceptions at the individual level. Results showed partial support for familiarity being positively associated with reliable responding. Moreover, high entitativity scores were associated with greater stigma perceptions at time 1 and time 2. Ongoing research on these indicators may be important in crafting future anti-stigma programs for leprosy.

Mycobacterium leprae and Mycobacterium lepromatosis infection. A report of six multibacillary cases of leprosy in Dominican Republic.

Periche Fernández, J., Pou-Soarez, V., Arenas, R., Juárez-Duran, E., Luna-Rojas, S., Xicohtencatl-Cortes, J., Martínez-Chavarría, L., Martínez-Hernández, F., Hernández-Castro, R.
31-03-2022
Jpn J Infect Dis
https://doi.org/10.7883/yoken.JJID.2021.709

The causative agents of leprosy are Mycobacterium leprae and Mycobacterium lepromatosis. M. lepromatosis was found in 2008 to cause diffuse lepromatous leprosy in Mexican patients. The objective of this work was to identify M. leprae and M. lepromatosis in paraffin-embedded skin samples from Caribbean leprosy patients. A total of 6 skin samples were obtained from the Dominican Republic. All cases presented the multibacillary form; 5 cases were nodular lepromatous leprosy, and 1 case was borderline lepromatous leprosy. All patients received multidrug therapy. Molecular identification was achieved using the M. leprae-specific repetitive element (RLEP) for M. leprae and the hemN gene for M. lepromatosis. Mycobacterium leprae was identified in two lepromatous leprosy cases and 1 borderline lepromatous leprosy case; M. lepromatosis was found in 1 nodular lepromatous leprosy case. Both Mycobacterium species were present in two nodular lepromatous leprosy cases. This is the first report of M. lepromatosis in the Dominican Republic.

Family-based intervention for prevention and self-management of disabilities due to leprosy, podoconiosis and lymphatic filariasis versus usual care in Ethiopia: study protocol for a cluster-randomised controlled trial.

van 't Noordende, A., Aycheh, M., Moges, N., Tadesse, T., Schippers, A.
30-03-2022
BMJ Open
https://doi.org/10.1136/bmjopen-2021-056620

Leprosy, podoconiosis and lymphatic filariasis (LF) are three skin-related neglected tropical diseases. All three conditions can lead to temporary and permanent impairments. These impairments progressively worsen and are major determinants of stigma, discrimination and participation restrictions. Self-care is essential to prevent disabilities and chronic disease complications. Many persons with leprosy-related, LF-related and podoconiosis-related disabilities need to practice self-management routines their entire life. This is difficult without support and encouragement of others. The objective of this study was to assess the effectiveness of a family-based intervention in terms of physical outcomes related to prevention and self-management of disabilities due to leprosy, podoconiosis and LF and family quality of life and well-being compared with usual practice and care. The study will use a cluster-randomised controlled trial design with two study arms. The project will be carried out in endemic districts in East and West Gojjam zones in the Amhara region in Ethiopia. Clusters consist of kebeles (lower administrative structures in the district) that have been merged, based on their geographical proximity and the number of cases in each kebele. A total of 630 participants will be included in the study. The intervention group will consist of 105 persons affected by leprosy, 105 persons affected by LF or podoconiosis, and 210 family members. The control group will consist of 105 persons affected by leprosy and 105 persons affected by LF or podoconiosis. The family-based intervention comprises an essential care package that consists of the following three main components: (1) self-management of disabilities, (2) economic empowerment and (3) psychosocial support. Participants in the control areas will receive usual practice and care. Data analysis includes, but is not limited to, calculating the percentage of change and corresponding 95%CI of physical impairment outcomes in each group, before and after the intervention is implemented, effect sizes, intention to treat and difference in difference analysis. Ethical approval has been obtained from the Debre Markos University Health Sciences Institutional Research Ethics Review Committee. Results will be disseminated through peer-reviewed publications, conference presentations and workshops. PACTR202108907851342.

Lepromatous leprosy with dermatofibroma features: colonization or morphological variant of histoid leprosy with epidermal induction?

Outi Pontes, C., Lourenco Pontes, A., Ocanha-Xavier, J., Xavier-Júnior, J.
29-03-2022
Int J Dermatol
https://doi.org/10.1111/ijd.16172

Leprosy is one of the main health problems in developing countries. It can show many different clinical presentations. A 37-yr-old woman with multiple reddish-brown papules on the lower and upper limbs, including the palms. The initial clinical impression was pityriasis lichenoides chronica. Biopsies were taken. The specimen from the left shin showed classical histological features of lepromatous leprosy. The specimen from the left thigh was similar to lipidized dermatofibroma showing epidermal hyperplasia with basal layer hyperpigmentation, a narrow Grenz zone, and spindle xanthomatous cells among dermal fibers. Fite-Faraco staining revealed many bacilli. No matter the clinical presentation, in the presence of lipidized macrophages, Fite-Faraco staining (an inexpensive method available worldwide) should be performed to rule out leprosy, even in nonendemic areas or associated with a tumor.

Somalia tackles leprosy and visceral leishmaniasis.

Bagcchi, S.
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Lancet Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35338873

IL-21 plays an important role in modulating "Th17-Treg" cell axis in leprosy Type 1 reactions.

Saini, C., Sapra, L., Bhardwaj, A., Tarique, M., Sharma, A., Khanna, N., Ramesh, V., Puri, P., Srivastava, R.
10-02-2022
Cytokine
https://pubmed.ncbi.nlm.nih.gov/35151928

Leprosy type 1 reaction (T1R) is a cell-mediated inflammatory reaction which involves skin and peripheral nerves in leprosy. Lesions with T1R have higher production of IL-17 cytokine from $CD4^+$ T cells along with lower TGF-β producing $FOXP3^+$ $CD4^+$ Tregs. IL-21 is an important cytokine that promotes the development and stability of Th17 cells in an autocrine manner. It can play an important role in the pathogenesis of T1R in leprosy. However, the mechanism by which IL-21 influences the pathogenic progress of leprosy T1R remains poorly understood. In the present study, we evaluated the expression of IL-21 cytokine in skin lesions of both non-reactional (NR) and T1R via immuno-histochemistry and quantitative PCR (qPCR). Further, expression of various genes (IL-17A, IL-17F, TGF-β, FOXP3, RORC and IL-21) was also measured by qPCR in cultured cells. We also analyzed the secretion of various cytokines such as of IL-21, IL-17A/F and TGF-β in the culture supernatants by ELISA. In addition, differentiation of Th17 and Treg cells were studied in PBMC cultures after stimulation with Mycobacterium leprae sonicated antigens and rIL-21 for 48 hrs and the phenotypes of Th17 and Tregs were determined by flowcytometric analysis. Our results clearly indicate that $IL\text{-}21^+$T cells were significantly higher in both peripheral blood and skin lesions of T1R as compared to NR patients. Moreover, we observed that recombinant IL-21 cytokine inhibited TGF-β producing Treg cells differentiation along with up-regulating Th17 cells under in-vitro conditions. The gene expression of IL-21 was significantly negatively correlated with Treg and positively correlated with Th17 cell markers in T1R patients. Our results suggested that IL-21 promotes T1R mediated inflammation via modulating the balance of Th17 and Treg cell populations.

TN strain proteome mediated therapeutic target mapping and multi-epitopic peptide-based vaccine development for Mycobacterium leprae.

Bhattacharya, M., Sharma, A., Ghosh, P., Patra, P., Mallick, B., Patra, B., Lee, S., Chakraborty, C.
09-02-2022
Infect Genet Evol
https://pubmed.ncbi.nlm.nih.gov/35150891

Leprosy is a significant universal health problem that is remarkably still a concern in developing countries due to infection frequency. New therapeutic molecules and next-generation vaccines are urgently needed to accelerate the leprosy-free world. In this direction, the present study was performed using two routes: proteome-mediated therapeutic target identification and mapping as well as multi-epitopic peptide-based novel vaccine development using state of the art of computational biology for the TN strain of M. leprae. The TN strain was selected from 65 Mycobacterium strains, and TN strain proteome mediated 83 therapeutic protein targets were mapped and characterized according to subcellular localization. Also, drug molecules were mapped with respect to protein targets localization. The Druggability potential of proteins was also evaluated. For multi-epitope peptide-based vaccine development, the four common types of B and T cell epitopes were identified (SLFQSHNRK, VVGIGQHAA, MMHRSPRTR, LGVDQTQPV) and combined with the suitable peptide linker. The vaccine component had an acceptable protective antigenic score (0.9751). The molecular docking of vaccine components with TLR4/MD2 complex exhibited a low ACE value (-244.12) which signifies the proper binding between the two molecules. The estimated free Gibbs binding energy ensured accurate protein-protein interactions (-112.46 kcal/mol). The vaccine was evaluated through adaptive immunity stimulation as well as immune interactions. The molecular dynamic simulation was carried out by using CHARMM topology-based parameters to minimize the docked complex. Subsequently, the Normal Mode Analysis in the internal coordinates showed a low eigen-value (1.3982892e-05), which also signifies the stability of molecular docking. Finally, the vaccine components were adopted for reverse transcription and codon optimization in E. coli strain K12 for the pGEX-4T1 vector, which supports in silico cloning of the vaccine components against the pathogen. The study directs the experimental study for therapeutics molecules discovery and vaccine candidate development with higher reliability.

Mycobacterial skin infection.

Gardini, G., Gregori, N., Matteelli, A., Castelli, F.
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Curr Opin Infect Dis
https://doi.org/10.1097/QCO.0000000000000820

The aim of this article is to review the most recent evidences concerning mycobacterial skin infections, limiting the period of literature research to 2020--2021. Mycobacterial skin infections include a heterogeneous group of cutaneous diseases.Cutaneous tuberculosis is usually the result of hematogenous dissemination or spread from underlying foci and it must be distinguished from tuberculids, resulting from the immunological reaction to Mycobacterium tuberculosis antigens. Leprosy prevalence was drastically reduced after introduction of multidrug therapy in the 1980s, but cases are still reported due to underdiagnosis, and animal and environmental reservoirs. Recent advances concentrate in the diagnostic field. Specific guidelines for the treatment of nontuberculous mycobacteria skin infections are missing and surgical procedures may be required. Prognosis is better as compared to nontuberculous mycobacteria lung disease. Rapid laboratory-confirmed diagnosis of Buruli ulcer may be achieved by the IS2404 PCR. Among new drugs, telacebec is promising in terms of potency, shorter duration and tolerability in animal studies. A clinical trial in humans is planned. Mycobacterial cutaneous lesions are nonpathognomonic and clinical suspicion must be confirmed by culture or molecular detection. Long-course multidrug

treatment is required based on susceptibility tests. Surgical intervention may also be required. Rehabilitation and psychosocial support reduce long-term physical and mental consequences mostly in Buruli ulcer and leprosy.

TRYPANOSOMES (TRYPANOSOMIASE ET MALADIE DE CHAGAS)

Development of novel dipeptide nitriles as inhibitors of rhodesain of Trypanosoma brucei rhodesiense.

Di Chio, C., Previti, S., Amendola, G., Ravichandran, R., Wagner, A., Cosconati, S., Hellmich, U., Schirmeister, T., Zappalà, M., Ettari, R.
29-03-2022
Eur J Med Chem
https://pubmed.ncbi.nlm.nih.gov/35385806

In this paper, we developed a new series of dipeptide nitriles that were demonstrated to be reversible rhodesain inhibitors at nanomolar level, with EC_{50} values against cultured T. b. brucei in the micromolar range. We also proved that our dipeptide nitriles directly bind to the active site of rhodesain acting as competitive inhibitors. Within the most interesting compounds, the dipeptide nitrile 2b showed the highest binding affinity towards rhodesain (K_i = 16 nM) coupled with a good antiparasitic activity (EC_{50} = 14.1 μM). Moreover, for the dipeptide nitrile 3e, which showed a K_i = 122 nM towards the trypanosomal protease, we obtained the highest antiparasitic activity (EC_{50} = 8.8 μM). Thus, given the obtained results both compounds could certainly represent new lead compounds for the discovery of new drugs to treat Human African Trypanosomiasis.

[Prevalence of infection markers and associated factors in donors of a peruvian blood bank].

More-Yupanqui, M., Canelo-Marruffo, P., Miranda-Watanabe, M., León-Herrera, A., Díaz-Romano, G., Sulca-Huamaní, O., Narrea-Cango, A., Pinedo-Torres, I.
01-04-2022
Rev Peru Med Exp Salud Publica
https://doi.org/10.17843/rpmesp.2021.384.9286

We aimed to determine the prevalence of infection markers in donors of a Peruvian blood bank and to assess whether donor sociodemographic variables are associated with the presence of these markers. An analytical cross-sectional study was carried out in 5942 donors of a blood bank, whose data was collected during 2018. Positivity to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) and HTLV I-II was determined, in addition to syphilis and Chagas disease. The prevalence of HIV was 0.81%; for HBV it was 6.19%; for HCV, 0.12%; for HTLV I-II, 0.66%; for Chagas disease, 2.76% and for syphilis it was 1.73%. Several sociodemographic factors were associated with infection markers positivity. The predominant donation type was non-voluntary (96%) and 53% had history of previous donation. The prevalence of infection markers for HIV, HBV, Chagas disease and syphilis in blood donors was high compared to other countries in the region.

Bioactivity of Natural Polyphenols as Antiparasitic Agents and their Biochemical Targets.

Soto-Sánchez, J.
04-04-2022
Mini Rev Med Chem
https://doi.org/10.2174/1389557522666220404090429

Leishmaniasis and trypanosomiasis are diseases that affect public health worldwide due to their high incidence, morbidity, and mortality. Available treatments are costly, prolonged, and toxic, not to mention the problem of parasite resistance. The development of alternative treatments is justified and polyphenols show promising activity. The main aim of this mini-review was to analyze the most promising phenolic compounds with reported antileishmanial and antitrypanosomal activity as well as their mechanisms of action. We found that the mode of action of these natural compounds mainly lignans, neolignans, and flavonoids depends on the organism they act on and includes, macrophage activation, induction of morphological changes such as chromatin condensation, DNA fragmentation, accumulation of acidocalcisomes, and glycosomes, Golgi damage and mitochondrial dysfunction as well as negative regulation of mitochondrial enzymes and other essential enzymes for parasite survival such as arginase. This gives a wide scope for future research towards the rational development of anti-kinetoplastid drugs. Although the specific molecular targets, bioavailability, route of administration, and dosages of some of these natural compounds need to be determined, polyphenols and their combinations represent a very promising and safe strategy to be considered for use against Leishmania spp and Trypanosoma spp. In addition, these compounds may provide a scaffold for developing new, more potent, and more selective antiprotozoal agents.

Prevalence of Chagas disease and strongyloidiasis among HIV-infected Latin American immigrants in Italy - The CHILI study.

Rodari, P., Tamarozzi, F., Tais, S., Degani, M., Perandin, F., Buonfrate, D., Nicastri, E., Lepore, L., Giancola, M., Carrara, S., Tavelli, A., Cozzi-Lepri, A., D'Arminio Monforte, A., Silva, R., Angheben, A.
31-03-2022
Travel Med Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35367666

Screening HIV-positive migrants for neglected tropical diseases having potential for life-threatening reactivation, such as Chagas disease and strongyloidiasis is not widely implemented. We evaluated the prevalence of these

infections among a large cohort of HIV-infected migrants from Latin America living in Italy. Cross-sectional study evaluating the prevalence of Trypanosoma cruzi and Strongyloides stercoralis infections in HIV-infected migrants from Latin America enrolled in the Italian Cohort of Antiretroviral-Naïve patients (ICONA) between 1997-2018, based on serology performed on sera stored in the ICONA Foundation biobank. Screening for Chagas disease was performed using two commercial ELISA complemented by commercial Immunoblot and CLIA if discordant. Strongyloidiasis was evaluated using a commercial ELISA. 389 patients were analysed. Fifteen (3.86%) had at least one positive Chagas ELISA test. Prevalence of Chagas disease was 0.5% or 1.29% depending on the confirmatory technique. Serology for strongyloidiasis was positive in 16 (4.11%) patients. Only Nadir $CD4^+$ T cell count was associated with discordant serology for Chagas disease ($p = 0.046$). The accuracy of seroassays for Chagas disease and strongyloidiasis in HIV-positive patients is unclear. To avoid missing potentially life-threatening infections, we suggest implementing additional diagnostic strategies in at-risk patients with inconclusive serology results.

Ruthenium metallotherapeutics: novel approaches to combatting parasitic infections.

Britten, N., Butler, J.
01-04-2022
Curr Med Chem
https://doi.org/10.2174/0929867329666220401105444

Human parasitic infections cause a combined global mortality rate of over one million people per annum and represent some of the most challenging diseases for medical intervention. Current chemotherapeutic strategies often require prolonged treatment, coupled with subsequent drug-induced cytotoxic morbidity to the host, while resistance generation is also a major concern. Metals have been used extensively throughout the history of medicine, with more recent applications as anticancer and antimicrobial agents. Ruthenium metallotherapeutic antiparasitic agents are highly effective at targeting a range of key parasites, including the causative agents of malaria, trypanosomiasis, leishmaniasis, amoebiasis, toxoplasmosis and other orphan diseases, while demonstrating lower cytotoxicity profiles than current treatment strategies. Generally, such compounds also demonstrate activity against multiple cellular target sites within parasites, including inhibition of enzyme function, cell membrane perturbation, and alterations to metabolic pathways, therefore reducing the opportunity for resistance generation. This review provides a comprehensive and subjective analysis of the rapidly developing area of ruthenium metal-based antiparasitic chemotherapeutics, in the context of rational drug design and potential clinical approaches to combatting human parasitic infections.

Variation in the Mitochondrial Genome of the Chagas Disease Vector Triatoma infestans (Hemiptera: Reduviidae).

Fernández, C., García, B.
31-03-2022
Neotrop Entomol
https://doi.org/10.1007/s13744-022-00953-y

Chagas' disease is transmitted mainly by members of the subfamily Triatominae (Hemiptera: Reduviidae). Among them, Triatoma infestans (Klug) is the main vector of the disease in Southern Cone of Latin America. In order to contribute to knowledge of the genetic variation between triatomine vectors, in the present study, we analyzed the intraspecific and interspecific variations of the seven mitogenomes available from Triatominae. In addition, in order to examine their evolutionary relationships with others species of Reduviidae and to estimate the divergence time of the main lineages, we constructed phylogenetic trees including mitogenome sequences of 30 species from Reduviidae. Comparative analysis between mitochondrial DNA sequences from two specimens of T. infestans revealed a total of 54 variable sites. Triatoma infestans, Triatoma dimidiata (Latreille), Triatoma rubrofasciata (De Geer), Triatoma migrans (Breddin), Rhodnius pictipes (Stål), and Panstrongylus rufotuberculatus (Champion) present similar mitogenome organization and the length differences observed among these species are primarily caused by variations in control region (CR) and intergenic spacers (IGS). The relative synonymous codon usage values (RSCU) were similar in the six species of Triatominae, and in agreement with the observed in other insects, a biased use of A and C nucleotides in the majority strand was detected. The monophyly of five subfamilies was strongly supported (Phymatinae, Peiratinae, Triatominae, Stenopodainae, and Harpactorinae), while the sampled species of Reduviinae were grouped with one specie from the Salyavatinae subfamily. The oldest subfamily is Phymatinae at 100.3 Mya (99.6-102.2 Mya) and the youngest is Triatominae and Stenopodainae at 52.6 Mya (42.5-63.7 Mya). The estimated diversification time for the Triatominae subfamily agrees with the Andean uplift geological event. An analysis with more mitogenomes from more Triatominae species would be necessary to provide sufficient evidence to support this finding.

Atypical human trypanosomosis: Potentially emerging disease with lack of understanding.

Revue de littérature

Kumar, R., Gupta, S., Bhutia, W., Vaid, R., Kumar, S.
30-03-2022
Zoonoses Public Health
https://doi.org/10.1111/zph.12945

Trypanosomes are the hemoflagellate kinetoplastid protozoan parasites affecting a wide range of vertebrate hosts having insufficient host specificity. Climatic change, deforestation, globalization, trade agreements, close association and genetic selection in links with environmental, vector, reservoir and potential susceptible hosts' parameters have led to emergence of atypical human trypanosomosis (a-HT). Poor recording of such neglected tropical disease, low awareness in

health professions and farming community has approached a serious intimidation for mankind. Reports of animal Trypanosoma species are now gradually increasing in humans, and lack of any compiled literature has diluted the issue. In the present review, global reports of livestock and rodent trypanosomes reported from human beings are assembled and discrepancies with the available literature are discussed along with morphological features of Trypanosoma species. We have described 21 human cases from the published information. Majority of cases 10 (47%) are due to T. lewisi, followed by 5 (24%) cases of T. evansi, 4 (19%) cases of T. brucei and 1 (5%) case each of T. vivax and T. congolense. Indian subcontinent witnessed 13 cases of a-HT, of which 9 cases are reported from India, which includes 7 cases of T. lewisi and 2 cases of T. evansi. Apart from, a-HT case reports, epidemiological investigation and treatment aspects are also discussed. An attempt has been made to provide an overview of the current situation of atypical human trypanosomosis caused by salivarian animal Trypanosoma globally. The probable role of Trypanosoma lytic factors (TLF) present in normal human serum (NHS) in providing innate immunity against salivarian animal Trypanosoma species and the existing paradox in medical science after the finding on intact functional apolipoprotein L1 (ApoL1) in Vietnam T. evansi Type A case is also discussed to provide an update on all aspects of a-HT. Insufficient data and poor reporting in Asian and African countries are the major hurdle resulting in under-reporting of a-HT, which is a potential emerging threat. Therefore, concerted efforts must be directed to address attentiveness, preparedness and regular surveillance in suspected areas with training of field technicians, medical health professionals and veterinarians. Enhancing a one health approach is specifically important in case of trypanosomosis.

Parasite load evaluation by qPCR and blood culture in Chagas disease and HIV co-infected patients under antiretroviral therapy.

Marcon, G., Ferreira, J., de Almeida, E., Delicio, A., Pereira, M., Wanderley, J., Martins, L., Andrade, P., de Lima, R., Costa, S.
30-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010317

Chagas disease also known as American trypanosomiasis, is caused by Trypanosoma cruzi and transmitted by triatominae-contaminated feces. It is considered a neglected tropical disease that affects 6 to 7 million people worldwide. The reactivation of Chagas disease occurs when the chronically infected hosts are not able to control T. cruzi infection, generating recurrence of the acute phase. HIV is the main immunosuppressive infection that can lead to the reactivation of chronic Chagas disease in AIDS conditions. In co-infected patients, the reactivation of Chagas disease is related to their high parasite load, high HIV viral load, and CD4 T-cell counting less than 200/mm3, which may evolve to meningoencephalitis and myocarditis. Eight T. cruzi/HIV co-infected patients under antiretroviral therapy (ART) and ten Chagas disease patients without HIV infection that attended at Study Group of Chagas Disease, Hospital de Clínicas, University of Campinas (GEdoCh/HC/UNICAMP-SP) and Pontifical Catholic University of Campinas SP (PUCC/SP) were evaluated. Tests for Chagas disease were performed, such as qPCR and T. cruzi blood culture. The patient's medical records were analyzed to verify clinical and epidemiological data, viral load, and CD4 T-cell counting since the outset of ART. For both groups, we found no statically significant differences between parasite load via blood culture and qPCR. In T. cruzi/HIV co-infected subjects, we observed a significant increase of CD4 T-cells counting and viral load decrease, which became undetectable over the years after ART. Parasites isolated from the patient's blood culture were genotyped, being the majority of them infected with TcII and one case of mixed infection (TcII and TcV/TcVI). These results were expected according to the region of origin of the patients. We suggest that the parasite load be monitored through qPCR in T.cruzi/HIV co-infected patients. We conclude that ART in people living with HIV improves infection and immunosuppression control, enabling the natural evolution of the American trypanosomiasis.

Natural compounds based chemotherapeutic against Chagas disease and leishmaniasis: mitochondrion as a strategic target.

Lazarin-Bidóia, D., Garcia, F., Ueda-Nakamura, T., Silva, S., Nakamura, C.
30-03-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35352776

Over the past years, natural products have been explored in order to find biological active substances to treat various diseases. Regarding their potential action against parasites such as trypanosomatids, specially Trypanosoma cruzi and Leishmania spp., much advance has been achieved. Extracts and purified molecules of several species from genera Piper, Tanacetum, Porophyllum, and Copaifera have been widely investigated by our research group and exhibited interesting antitrypanosomal and antileishmanial activities. These natural compounds affected different structures in parasites, and we believe that the mitochondrion is a strategic target to induce parasite death. Considering that these trypanosomatids have a unique mitochondrion, this cellular target has been extensively studied aiming to find more selective drugs, since the current treatment of these neglected tropical diseases has some challenges such as high toxicity and prolonged treatment time. Here, we summarise some results obtained with natural products from our research group and we further highlighted some strategies that must be considered to finally develop an effective chemotherapeutic agent against these parasites.

Clinical trials as disease control? The political economy of sleeping sickness in the Democratic Republic of the Congo (1996-2016).

Falisse, J., Mpanya, A.
08-03-2022

Soc Sci Med
https://pubmed.ncbi.nlm.nih.gov/35299059

Human African Trypanosomiasis (HAT), commonly known as sleeping sickness, is closer than ever to being eliminated as a public health problem. The main narratives for the impressive drop in cases allude to drugs discovery and global financing and coordination. They raise questions about the relationship between well-funded international clinical research and much less well-endowed national disease control programmes. They need to be complemented with a solid understanding of how (and why) national programmes that do most of the frontline work are structured and operate. We analyse archives and in-depth interviews with key stakeholders and explore the role the national HAT programme played in the Democratic Republic of the Congo (DRC), a country that consistently accounts for over 60% of HAT cases worldwide. The programme grew strongly between 1996, when it was barely surviving, and 2016. Our political economy lens highlights how the leadership of the programme managed to carve itself substantial autonomy within the health system, forged new international alliances, and used clinical trials and international research to not only improve treatment and diagnosis but also to enhance its under-resourced disease control system. The DRC, a country often described as 'fragile', stands out as having an efficient national HAT programme that made full use of a window of opportunity that arose in the early 2000s when international researchers and donors responded to the ambition to simplify disease control and make HAT treatment more humane. We discuss the sustainability of both the vertical approach embodied in the DRC's national HAT programme and its funding model at a time when the number of HAT cases is at an all-time low and better integration within the health system is urgent. Our study provides insights for collaborations between unevenly-resourced international research efforts and national health programmes.

Nasal immunization with a L. lactis-derived trans-sialidase antigen plus c-di-AMP protects against acute oral T. cruzi infection.

Pacini, M., González, F., Dinatale, B., Bulfoni Balbi, C., Villar, S., Farré, C., Lupi, G., Espariz, M., Blancato, V., Magni, C., Marcipar, I., Pérez, A.
09-03-2022
Vaccine
https://pubmed.ncbi.nlm.nih.gov/35279330

The new generation of vaccines for Chagas disease, are focused to induce both humoral and cellular response to effectively control Trypanosoma cruzi parasites. The administration of vaccine formulations intranasally has the advantage over parenteral routes that can induce a specific response at mucosal and systemic levels. This study aimed to evaluate and compare the immunogenicity and prophylactic effectiveness of two Trans-sialidase (TS)-based mucosal vaccines against T. cruzi administered intranasally. Vaccines consisted of a recombinant fragment of TS expressed in Lactococcus lactis formulated in two different adjuvants. The first, was an immunostimulant particle (ISPA, an ISCOMATRIX-like adjuvant), while the second was the dinucleotide c-di-AMP, which have shown immunostimulant properties at the mucosal level. BALB/c mice were immunized intranasally (3 doses, one every two weeks) with each formulation (TS + ISPA or TS + c-di-AMP) and with TS alone or vehicle (saline solution) as controls. Fifteen days after the last immunization, both TS + ISPA or TS + c-di-AMP induced an evident systemic humoral and cellular response, as judged by the increased plasma anti-TS IgG2a titers and IgG2a/IgG1 ratio and enhanced cellular response against TS. Plasma derived antibodies from TS + c-di-AMP also inhibit in vitro the invasion capacity of T. cruzi. Furthermore, specific secretory IgA was more enhanced in TS + c-di-AMP group. Protective efficacy was proved in vaccinated animals by an oral T. cruzi-challenge. Parasitemia control was only achieved by animals vaccinated with TS + c-di-AMP, despite all vaccinates groups showed enhanced $CD8^{+}IFN\text{-}\gamma^{+}$ T cell numbers. In addition, it was reflected during the acute phase in a significant reduction of tissue parasite load, clinical manifestations and diminished tissue damage. The better prophylactic capacity elicited by TS + c-di-AMP was related to the induction of neutralizing plasma antibodies and augmented levels of mucosal IgA since TS + ISPA and TS + c-di-AMP groups displayed similar immunogenicity and $CD8^{+}IFN\text{-}\gamma^{+}$ T-cell response. Therefore, TS + c-di-AMP formulation appears as a promising strategy for prophylaxis against T. cruzi.

A dataset of proteins associated with *Trypanosoma cruzi LYT1* mRNAs.

Márvez, E., Segura, C., Requena, J., Puerta, C.
15-02-2022
Data Brief
https://doi.org/10.1016/j.dib.2022.107953

Post-transcriptional gene regulation in *Trypanosoma cruzi*, the etiological agent of Chagas disease, plays a critical role in ensuring that the parasite successfully completes its life cycle in both of its obligate hosts: insect vector and mammals. This regulation is basically governed by RNA binding proteins (RBPs) through their interactions with *cis*-elements located in the UTRs of their mRNA targets. LYT1 gene, coding for a virulence factor of *T. cruzi*, is expressed into two isoforms: kLYT1 and mLYT1, which play different functions according to their cellular location and parasite life-cycle stages. Whereas kLYT1 exhibits a regulatory role during the epimastigote-to-metacyclic trypomastigote stage transition, mLYT1 acts as a pore-forming protein, relevant for host cell invasion and parasite intracellular survival. Considering the LYT1 biological relevance and the fact that this is a protein exclusive of *T. cruzi*, the protein and its mechanisms regulating the alternative gene expression products are promising targets for therapeutic intervention. In this work, an experimental approach consisting of pull-downs assays followed by proteomic analyzes was carried out to identify the proteins interacting with the different LYT1 mRNAs. The dataset presented here was obtained through three biological

replicates using all the different UTRs characterized in the LYT1 mRNAs (i.e., 5´UTR kLYT1, 5´UTR mLYT1, and I and II-type 3´UTRs) as baits, and protein extracts from epimastigotes and trypomastigotes of the 058 PUJ (DTU I) strain. Bound proteins were analyzed by liquid chromatography coupled to mass spectrometry (LC/MS). As a control of non-specificity, the same protein extracts were incubated with *Leishmania braziliensis* rRNA and the bound proteins also identified by LC/MS. In all, 1,557 proteins were identified, 313 of them were found in at least two replicates and 18 proteins were exclusively associated with the LYT1 baits. Of these, six proteins have motifs related to RNA binding, and seven remain annotated as hypothetical proteins. Remarkably, three of these hypothetical proteins also contain nucleic acid binding motifs. This knowledge, beside expanding the known *T. cruzi* proteome, gains insight into putative regulatory proteins responsible for alternative LYT1 mRNAs processing. Raw mass spectrometry data are available via MassIVE proteome Xchange with identifier PXD027371.

Phylogenetic diversity of two common Trypanosoma cruzi lineages in the Southwestern United States.

Flores-López, C., Mitchell, E., Reisenman, C., Sarkar, S., Williamson, P., Machado, C.
17-02-2022
Infect Genet Evol
https://pubmed.ncbi.nlm.nih.gov/35183751

Trypanosoma cruzi is the causative agent of Chagas disease, a devastating parasitic disease endemic to Central and South America, Mexico, and the USA. We characterized the genetic diversity of Trypanosoma cruzi circulating in five triatomine species (Triatoma gerstaeckeri, T. lecticularia, T.indictiva, T. sanguisuga and T. recurva) collected in Texas and Southern Arizona using multilocus sequence typing (MLST) with four single-copy loci (cytochrome oxidase subunit II- NADH dehydrogensase subunit 1 region (COII-ND1), mismatch-repair class 2 (MSH2), dihydrofolate reductase-thymidylate synthase (DHFR-TS) and a nuclear gene with ID TcCLB.506529.310). All T. cruzi variants fall in two main genetic lineages: 75% of the samples corresponded to T. cruzi Discrete Typing Unit (DTU) I (TcI), and 25% to a North American specific lineage previously labelled TcIV-USA. Phylogenetic and sequence divergence analyses of our new data plus all previously published sequence data from those four loci collected in the USA, show that TcIV-USA is significantly different from any other previously defined T. cruzi DTUs. The significant level of genetic divergence between TcIV-USA and other T. cruzi DTUs should lead to an increased focus on understanding the epidemiological importance of this DTU, as well as its geographical range and pathogenicity in humans and domestic animals. Our findings further corroborate the fact that there is a high genetic diversity of the parasite in North America and emphasize the need for appropriate surveillance and vector control programs for Chagas disease in southern USA and Mexico.

Trypanosoma cruzi, beyond the dogma of non-infection in birds.

Martínez-Hernández, F., Oria-Martínez, B., Rendón-Franco, E., Villalobos, G., Muñoz-García, C.
08-02-2022
Infect Genet Evol
https://pubmed.ncbi.nlm.nih.gov/35144004

Trypanosoma cruzi is a protozoan parasite responsible for Chagas disease affecting seven million people. The disease cycle is maintained between Triatominae insects and Mammalia hosts; a refractory effect against infection was noted in birds, but only verified in poultry. This paper presents a new host record for T. cruzi, the American barn-owl (Tyto furcata). Trypanosoma cruzi DTU II molecular evidence was found in heart, intestine, liver, and breast suggesting an established chronic infection based on the parasite DNA presence in multiple organs but absent in spleen, as in the murine model and chronically infected raccoons (Procyon lotor). For birds, the parasite rejection was explained based on the complement and high body temperature, but these mechanisms vary greatly among the members of the avian class. Therefore, there is a need to investigate whether more bird species can become infected, and if T. furcata has a role in disseminating, transmitting and/or maintaining the parasite.

Epidemiological aspects of Chagas disease in the state of Piauí (Northeast Brazil) in the period 2010-2019.

Santana, M., Leal, A., de Sousa, R., Brandão Dos Santos, L., Mascarenhas, M., Rodrigues, M., Mendonça, V.
31-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35114171

Chagas disease (ChD), caused by the hemoflagellate protozoan Trypanosoma cruzi, is an important morbidity that affects approximately six million people in the American continent. T. cruzi parasites are mainly transmitted to human by the infected feces of blood-sucking triatomine insects. The persistent disease is endemic in many regions of South America, mostly affecting residents of rural areas. The aim of this study was to evaluate epidemiological aspects of ChD in the state of Pi-auí located in northeastern Brazil. This is an analytical cross-sectional study carried out from the collection of data of the Notifiable Diseases Information System (SINAN, in Portuguese, Sistema de Informações de Agravos de Notificação) of suspected and confirmed cases of acute ChD in the state of Piauí, in the period 2010-2019. Associations between T. cruzi positivity and the study variables were determined by the chi-square test or Fisher's exact test and were raised as prevalence ratios (PR) with 95% confidence interval. According to this survey, 517 suspected cases of acute ChD were reported in Piauí, with 70 cases (13.5%) confirmed. In 88.5% of confirmed cases, confirmation occurred by laboratory diagnosis. Most of the confirmed cases occurred in municipalities located in the semiarid region, with the municipality of São João do Piauí presenting the highest

number of cases. Regarding sociodemographic data, females represent 55.7% of cases, people over 50 years of age (55.7%), being three cases in people up to 18 years of age, and less than 8 years of schooling (67.1%). 77.9% of confirmed cases had vector transmission as the probable form of infection. The data available in this study conclude that vectorial transmission of ChD in the state of Piauí remains active. This fact is corroborated by the number of notified and confirmed cases of acute ChD, requiring housing improvement programs and more effective epidemiological surveillance to control the transmission of the disease in the state.

Metavirome composition of Brazilian blood donors positive for the routinely tested blood-borne infections.

Bezerra, R., Ximenez, J., Giovanetti, M., Zucherato, V., Bitencourt, H., Zimmermann, A., Alcantara, L., Covas, D., Kashima, S., Slavov, S.
26-01-2022
Virus Res
https://pubmed.ncbi.nlm.nih.gov/35090996

Viral metagenomics is widely applied to characterize emerging viral pathogens but it can also reveal the virome composition in health and disease. The evaluation of the virome in healthy blood donors can provide important knowledge on possible transfusion threats. Currently, there is still a paucity of information regarding the virome of blood donors who test positive for routinely tested blood-borne infections. Such analysis may reveal co-infections which in turn appear to be crucial for transfusion medicine and for patient management. The aim of this study was to evaluate the metavirome in blood donors who tested positive for routinely tested blood-borne infections, the information for which is important for transfusion medicine and blood donor management. For this purpose, we analyzed 18 blood donations obtained from HIV and HBV-infected blood donors from the Brazilian Amazon (Amapa state) and 11 HIV, HBV, HCV, syphilis and Chagas disease - positive blood donations obtained from blood donors sampled in South Brazil (Rio Grande do Sul state). We additionally included a control group of 20 blood donors obtained from Southeast Brazil (State of São Paulo). Samples were assembled in pools and sequenced by the Illumina NovaSeq 6000 platform. To link a given virus with geographic region or type of blood donor, we performed supervised machine learning classification (fingerprint analysis). The virome of both locations was predominantly composed of commensal viruses. However, in HBV-infected blood donors from the Brazilian Amazon, the Human Pegivirus-1 (HPgV-1) reads were prevailing, while in HIV-infected donors from the same location, the torque teno virus (TTV) reads expressive abundance. In blood donors from South Brazil, the most abundant reads were classified as Human endogenous retrovirus K (HERV-K). Putative emerging viruses like the Human gemykibivirus-2 (HuGkV-2) were exclusively identified in samples from the Brazilian Amazon. The fingerprint analysis demonstrated that the HERV-K, TTV-7, 13, and 15 were statistically important for the infected blood donors, while TTV-5, 12 and 20 were linked to geographic localization. Our study revealed differences in the viral composition among blood donors who tested positive for routinely tested blood-borne infections from two different Brazilian regions and indicated the presence of putative emerging viruses in samples obtained from the Amazon. Together our results show that the presence of specific commensal viruses may be related donor infection status but additional investigations including larger study groups and samples from other Brazilian regions are needed to confirm this hypothesis.

Re: "Immunothrombotic dysregulation in chagas disease and COVID-19: a comparative study of anticoagulation".

Hasslocher-Moreno, A.
20-01-2022
Mol Cell Biochem
https://doi.org/10.1007/s11010-022-04361-z

4-nitrobenzoylcoumarin potentiates the antiparasitic, anti-inflammatory and cardioprotective effects of benznidazole in a murine model of acute Trypanosoma cruzi infection.

Vilas-Boas, D., Oliveira, R., Gonçalves-Santos, E., Silva, L., Diniz, L., Mazzeti, A., Brancaglion, G., Carvalho, D., Caldas, S., Novaes, R., Caldas, I.
15-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35038424

The anti-inflammatory and cardioprotective potential of coumarin metabolites in infectious myocarditis remains overlooked. Thus, the impact of the synthetic 4-nitrobenzoylcoumarin (4NB) alone and combined with benznidazole (Bz) in a murine model of Trypanosoma cruzi-induced acute myocarditis was investigated. Swiss mice infected with T. cruzi were randomized in 8 groups: uninfected, infected untreated or treated with 50 and 100 mg/kg 4NB or Bz alone and combined. Treatments were administered by gavage for 20 days. Cytokines (IL-2, IL-6, IL-10, IL-17, TNFα, and IFN-γ), immunoglobulin reactivity index (total IgG, IgG1, IgG2a and IgG2b), atrial natriuretic peptide (ANP), parasitemia, serum transaminases, heart and liver cellularity were analyzed. T. cruzi infection induced blood parasitism, heart and liver inflammation, upregulated all cytokines, IgG reactivity index, ANP and transaminase levels, determining 43% mortality in untreated mice. Transaminase levels, mean parasitemia, heart inflammation and ANP were reduced in 4NB-treated mice, reaching a 100% survival rate. Total survival (100%) was also obtained in all combinations of Bz and 4NB, which were effective in reducing blood parasitism, transaminases, cytokines and ANP levels, IgG reactivity index, liver and heart interstitial cellularity compared to 50 mg/kg Bz. Our findings indicated that 4NB alone and

combined with Bz was well tolerated, showing no evidence of hepatotoxicity. Mainly in combination, these drugs exerted protective effects against T. cruzi-induced acute myocarditis by attenuating blood parasitism, systemic and heart inflammation. Thus, combinations based on 4NB and Bz are potentially relevant to develop new and more effective drug regimens for the treatment of T. cruzi-induced myocarditis.

Optimization of physicochemical properties is a strategy to improve drug-likeness associated with activity: Novel active and selective compounds against Trypanosoma cruzi.

Varela, M., Amaral, M., Romanelli, M., de Castro Levatti, E., Tempone, A., Fernandes, J.
02-01-2022
Eur J Pharm Sci
https://pubmed.ncbi.nlm.nih.gov/34986415

Trypanosoma cruzi is the causing agent of Chagas disease, a parasitic infection without efficient treatment for chronic patients. Despite the efforts, no new drugs have been approved for this disease in the last 60 years. Molecular modifications based on a natural product led to the development of a series of compounds (LINS03 series) with promising antitrypanosomal activity, however previous chemometric analysis revealed a significant impact of excessive lipophilicity and low aqueous solubility on potency of amine and amide derivatives. Therefore, this work reports different modifications in the core structure to achieve adequate balance of the physicochemical properties along with biological activity. A set of 34 analogues were designed considering predicted properties related to lipophilicity/hydrosolubility and synthesized to assess their activity and selective toxicity towards the parasite. Results showed that this strategy contributed to improve the drug-likeness of the series while considerable impacts on potency were observed. The rational analysis of the obtained data led to the identification of seven active piperazine amides (28-34, IC_{50} 8.7 to 35.3 µM against intracellular amastigotes), devoid of significant cytotoxicity to mammalian cells. The addition of water-solubilizing groups and privileged substructures such as piperazines improved the physicochemical properties and overall drug-likeness of these compounds, increased potency and maintained selectivity towards the parasite. The obtained results brought important structure-activity relationship (SAR) data and new lead structures for further modifications were identified to achieve improved antitrypanosoma compounds.

Insights into CX3CL1/Fractalkine during experimental Trypanosoma cruzi infection.

Menezes, T., Machado, B., Toledo, D., Santos, P., Ribeiro, L., Talvani, A.
18-12-2021
Parasitol Int
https://pubmed.ncbi.nlm.nih.gov/34929405

Trypanosoma cruzi triggers a progressive myocarditis in mammalians through activation and recruitment of leukocytes and release of inflammatory mediators. The chemokine CX3CL1 has been highlighted for its potential role in the parasite controlling in end-pathological status of infected hosts. This study investigated the systemic and cardiac release of CX3CL1 in experimental T. cruzi infection and how this chemokine correlates with endothelin-1 and TNF. Male Fisher rats (n = 20) were infected, or not, by the Y strain of T. cruzi and parasitemia was daily evaluated and immunoassays performed in the cardiac tissue macerated supernatant and in serum to evaluate CX3CL1, endothelin, and TNF production on days 5 and 15 of infection. T. cruzi infection induced a higher serum and cardiac production of these mediators on days 5 and 15 of infection. In both periods of infection, respectively, CX3CL1 showed a positive correlation with TNF ($r = 0.833$, $p < 0.001$ and $r = 0.723$, $p < 0.001$) and endothelin-1 ($r = 0.801$, $p < 0.05$ and $r = 0.857$, $p < 0.001$), which reinforce its participation in the T. cruzi-induced myocarditis development.

Irreversible inhibitors of the proline racemase unveil innovative mechanism of action as antibacterial agents against Clostridioides difficile.

Gateau, C., Melo, G., Uriac, P., Tasseau, O., Renault, J., Blondel, A., Gouault, N., Barbut, F., Minoprio, P.
05-01-2022
Chem Biol Drug Des
https://doi.org/10.1111/cbdd.14005

Proline racemases (PRAC), catalyzing the l-proline and d-proline interconversion, are essential factors in eukaryotic pathogens such as Trypanosoma cruzi, Trypanosoma vivax, and Clostridioides difficile. If the discovery of irreversible inhibitors of T. cruzi PRAC (TcPRAC) led to innovative therapy of the Chagas disease, no inhibitors of CdPRAC have been discovered to date. However, C. difficile, due to an increased incidence in recent years, is considered as a major cause of health threat. In this work, we have taken into account the similarity between TcPRAC and CdPRAC enzymes to design new inhibitors of CdPRAC. Starting from (E) 4-oxopent-2-enoic acid TcPRAC irreversible inhibitors, we synthesized 4-aryl substituted analogs and evaluated their CdPRAC enzymatic inhibition against eleven strains of C. difficile. This study resulted in promising candidates and allowed for identification of (E)-4-(3-bromothiophen-2-yl)-4-oxobut-2-enoic acid 20 that was chosen for complementary in vivo studies and did not reveal in vivo toxicity.

Surveillance and genotype characterization of zoonotic trypanosomatidae in *Didelphis marsupialis* in two endemic sites of rural Panama.

Pineda, V., González, K., Perea, M., Rigg, C., Calzada, J., Chaves, L., Vásquez, V., Samudio, F., Gottdenker, N., Saldaña, A.
06-12-2021
Int J Parasitol Parasites Wildl
https://doi.org/10.1016/j.ijppaw.2021.12.002

Didelphis marsupialis has been reported as a competent reservoir for trypanosomatid parasites infections. The aim of this study was to measure *Trypanosoma cruzi, T. rangeli,* and *Leishmania* spp. infection rates and to characterize discrete typing units (DTUs) of *T. cruzi* in *D. marsupialis* from two Chagas disease endemic sites in Panama. Blood from 57 wild-caught *D. marsupialis* were examined from two rural communities, Las Pavas (N = 18) and Trinidad de las Minas (N = 39). Twenty-two (38.60%) opossums were positive for flagellates by general hemoculture. *T. cruzi* infection was confirmed by positive hemoculture and/or kDNA based PCR performed in 31/57 (54.39%) blood samples from opossums. *T. rangeli* infection was confirmed by hemoculture and/or TrF/R2-Primer PCR assay applied on 12/57 (21.05%) blood samples. Nine (15.79%) *D. marsupialis* harbored *T. cruzi/T. rangeli* coinfections. All opossums tested negative for *Leishmania* spp. by PCR assays based on kDNA and HSP70 gene amplification. There was a significant association between *T. cruzi* infection and site (Fisher exact test, p = 0.02), with a higher proportion of *T. cruzi* infected opossums in Las Pavas (77.78%, n = 14/18) compared to Trinidad de las Minas (43.59%, n = 17/39). A significant association was found between habitat type and *T. cruzi* infection in opossums across both communities, (X^2 = 6.91, p = 0.01, df = 1), with a higher proportion of *T. cruzi* infection in opossums captured in forest remnants (76%, 19/25) compared to peridomestic areas (37.5%, 12/32). *T. rangeli* detection, but not *T. cruzi* detection, may be improved by culture followed by PCR. TcI was the only DTU detected in 22 *T. cruzi* samples using conventional and real-time PCR. Eight *T. rangeli* positive samples were characterized as KP1(-)/lineage C. Trypanosome infection data from this common synanthropic mammal provides important information for improved surveillance and management of Chagas disease in endemic regions of Panama.

Live attenuated vaccines, a favorable strategy to provide long-term immunity against protozoan diseases.

Revue de littérature

Solana, J., Moreno, J., Iborra, S., Soto, M., Requena, J.
09-12-2021
Trends Parasitol
https://pubmed.ncbi.nlm.nih.gov/34896016

The control of diseases caused by protozoan parasites is one of the United Nations' Sustainable Development Goals. In recent years much research effort has gone into developing a new generation of live attenuated vaccines (LAVs) against malaria, Chagas disease and leishmaniasis. However, there is a bottleneck related to their biosafety, production, and distribution that slows downs further development. The success of irradiated or genetically attenuated sporozoites against malaria, added to the first LAV against leishmaniasis to be evaluated in clinical trials, is indicative that the drawbacks of LAVs are gradually being overcome. However, whether persistence of LAVs is a prerequisite for sustained long-term immunity remains to be clarified, and the procedures necessary for clinical evaluation of vaccine candidates need to be standardized.

Evaluation of the effectiveness of fluralaner against adult stages of Rhodnius prolixus in dogs.

Ortega-Pacheco, A., Poot-Ramos, A., Chan-Pérez, J., Gutiérrez-Blanco, E., Acevedo-Arcique, C., Baak-Baak, C., Jiménez-Coello, M.
12-11-2021
Parasitol Int
https://pubmed.ncbi.nlm.nih.gov/34781015

Triatomines are vectors of American Trypanosomiasis also known as Chagas´ disease where several reservoirs including dogs are involved in the transmission cycle of the causal agent (Trypanosoma cruzi). Considering that the prevalence of American trypanosomiasis in dogs is higher than in humans and that dogs in addition are susceptible of this disease, and are involved in peridomestic transmission to humans, the search for new alternatives for vector control of the triatomines responsible for transmission in dogs is required. Over the 20 weeks the study lasted, 600 individual female, adult of Rhodnius prolixus were offered to the 15 dogs treated with a single oral dose of Fluralaner (Bravecto®, MSD). Feeding pattern of triatomines was not affected by the treatment during the whole study. The fluralaner-induced mortality of R. prolixus had a significant effect until week 12 at which time 100% mortality was observed. Mortality decreased to 67.5% at week 16 to practically nil 0.8% on week 20. Fluralaner achieved 100% mortality of triatomines between 12- and 48-h post-feeding. It was demonstrated that a single oral dose of fluralaner in dogs is highly effective in producing mortality in adult R. prolixus for the time guaranteed by the manufacturer for other blood-sucking insects, with a considerable effective residual effect for up to 16 weeks. Due to this high efficacy, fluralaner could be considered in strategies to control the transmission vectors of Chagas disease in dogs and in turn decrease the peri-domestic transmission cycle, particularly in hyperendemic areas.

LEISHMANIOSE

Febrifugine dihydrochloride as a new oral chemotherapeutic agent against visceral leishmaniasis infection.

Pandey, R., Ojha, R., Devender, M., Sebastian, P., Namdeo, M., Kumbhar, B., Sundar, S., Maurya, R., Prajapati, V.
04-04-2022
Exp Parasitol
https://pubmed.ncbi.nlm.nih.gov/35390313

Visceral leishmaniasis (VL) is the deadliest form of leishmaniasis without a safer treatment option. This study implies drug repurposing to find a novel antileishmanial

compound, namely febrifugine dihydrochloride (FFG) targeting Leishmania antioxidant system. Starting with virtual screening revealed the high binding affinity and lead likeness of FFG against the trypanothione reductase (TR) enzyme of Leishmania donovani, followed by experimental validation. The promastigotes inhibition assay gave the IC50 concentration of FFG and Miltefosine (positive control) as 7.16 ± 1.39nM and 11.41 ± 0.29 µM, respectively. Their CC_{50} was found as 451 ± 12.73nM and 135.9 ± 5.94 µM, respectively. FFG has been shown to increase the reactive oxygen species (ROS), leading to apoptosis-like cell death among L. donovani promastigotes. Spleen touch biopsy resulted in 62% and 55% decreased parasite load with FFG and miltefosine treatment, respectively. Cytokine profiling has shown an increased proinflammatory cytokine response post-FFG treatment. Moreover, FFG is safe on the liver toxicity parameter in mice post-treatment.

The effect of the sugar metabolism on Leishmania infantum promastigotes inside the gut of Lutzomyia longipalpis: A sweet relationship?

Hendrickx, S., Caljon, G.
06-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010293

It is well-known that Leishmania parasites can alter the behavior of the sand fly vector in order to increase their transmission potential. However, little is known about the contribution of the infecting host's blood composition on subsequent sand fly infection and survival. This study focused on the host's glucose metabolism and the insulin/insulin-like growth factor 1 (IGF-1) pathway as both metabolic processes are known to impact vector-parasite interactions of other protozoa and insect species. The focus of this study was inspired by the observation that the glycemic levels in the blood of infected Syrian golden hamsters inversely correlated to splenic and hepatic parasite burdens. To evaluate the biological impact of these findings on further transmission, Lutzomyia longipalpis sand flies were infected with blood that was artificially supplemented with different physiological concentrations of several monosaccharides, insulin or IGF-1. Normoglycemic levels resulted in transiently higher parasite loads and faster appearance of metacyclics, whereas higher carbohydrate and insulin/IGF-1 levels favored sand fly survival. Although the recorded effects were modest or transient of nature, these observations support the concept that the host blood biochemistry may affect Leishmania transmission and sand fly longevity.

Host cholesterol influences the activity of sterol biosynthesis inhibitors in Leishmania amazonensis.

Andrade-Neto, V., Manso, P., Pereira, M., de Cicco, N., Atella, G., Pelajo-Machado, M., Menna-Barreto, R., Torres-Santos, E.
04-04-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35384972

A significant percentage of exogenous cholesterol was found in promastigotes and amastigotes of all studied species of Leishmania, suggesting a biological role for this molecule. Previous studies have shown that promastigotes of Leishmania uptake more low-density lipoprotein (LDL) particles under pharmacological pressure and are more susceptible to ergosterol inhibition in the absence of exogenous sources of cholesterol. This work shows that the host's LDL is available to intracellular amastigotes and that the absence of exogenous cholesterol enhances the potency of sterol biosynthesis inhibitors in infected macrophages. A complete understanding of cholesterol transport to the parasitophorous vacuole can guide the development of a new drug class to be used in combination with sterol biosynthesis inhibitors for the treatment of leishmaniases.

Thymoquinone Induced Leishmanicidal Effect via Programmed Cell Death in *Leishmania donovani*.

Islamuddin, M., Ali, A., Afzal, O., Ali, A., Ali, I., Altamimi, A., Alamri, M., Kato, K., Parveen, S.
15-03-2022
ACS Omega
https://doi.org/10.1021/acsomega.2c00467

Visceral leishmaniasis (VL) or kala-azar is a vector-borne dreaded protozoal infection that is caused by the parasite *Leishmania donovani*. With increases in the dramatic infection rates, present drug toxicity, resistance, and the absence of an approved vaccine, the development of new antileishmanial compounds from plant sources remains the keystone for the control of visceral leishmaniasis. In this study, we evaluated the leishmanicidal effect of thymoquinone against *L. donovani* with an *in vitro* and *ex vivo* model. Thymoquinone exhibited potent antipromastigote activity with IC_{50} and IC_{90} concentrations achieved at 6.33 ± 1.21 and 20.71 ± 2.15 µM, respectively, whereas the IC_{50} and IC_{90} concentrations were found to be 7.83 ± 1.65 and 27.25 ± 2.20 µM against the intramacrophagic form of amastigotes, respectively. Morphological changes in promastigotes and growth reversibility study following treatment confirmed the leishmanicidal effect of thymoquinone. Further, thymoquinone exhibited leishmanicidal activities against *L. donovani* promastigote through cytoplasmic shrinkage, membrane blebbing, chromatin condensation, cellular and nuclear shrinkage, and DNA fragmentation, as observed under scanning and transmission electron microscopy analyses. The antileishmanial activity was exerted via programmed cell death as proved by exposure of phosphatidylserine, DNA nicking by TUNEL assay, and loss of mitochondrial membrane potential. Thymoquinone at a concentration of 200 µM was devoid of any cytotoxic effects against mammalian macrophage cells. Thymoquinone showed strong leishmanicidal activity against *L. donovani*, which is mediated via an apoptosis mode of parasitic cell death, and accordingly, thymoquinone may be the source of a new lead molecule for the cure of VL.

Thiazolidine derivatives: In vitro toxicity assessment against promastigote and amastigote forms of leishmania infantum and ultrastructural study.

Gouveia, A., Santos, F., Alves, L., Cruz-Filho, I., Silva, P., Jacob, I., Soares, J., Santos, D., Souza, T., Oliveira, J., Lima, M.
02-04-2022
Exp Parasitol
https://pubmed.ncbi.nlm.nih.gov/35381223

Neglected diseases, such as Leishmaniasis, constitute a group of communicable diseases that occur mainly in tropical countries. Considered a public health problem with limited treatment. Therefore, there is a need for new therapies. In this sense, our proposal was to evaluate in vitro two series of thiazolidine compounds (7a-7e and 8a-8e) against Leishmania infantum. We performed in vitro evaluations through macrophage cytotoxicity assays (J774) and nitric oxide production, activity against promastigotes and amastigotes, as well as ultrastructural analyzes in promastigotes. In the evaluation of cytotoxicity, the thiazolidine compounds presented CC_{50} values between 8.52 and 126.83 µM. Regarding the evaluation against the promastigote forms, the IC_{50} values ranged between 0.42 and 142.43 µM. Compound 7a was the most promising, as it had the lowest IC_{50}. The parasites treated with compound 7a showed several changes, such as cell body shrinkage, shortening and loss of the flagellum, intense mitochondrial edema and cytoplasmic vacuolization, leading the parasite to cell inviability. In assays against the amastigote forms, the compound showed a low IC_{50} (0.65 µM). These results indicate that compound 7a was efficient for both evolutionary forms of the parasite. In silico studies suggest that the compound has good oral bioavailability. These results show that compound 7a is a potential drug candidate for the treatment of Leishmaniasis.

Sand flies: Basic information on the vectors of leishmaniasis and their interactions with Leishmania parasites.

Revue de littérature

Cecílio, P., Cordeiro-da-Silva, A., Oliveira, F.
04-04-2022
Commun Biol
https://doi.org/10.1038/s42003-022-03240-z

Blood-sucking arthropods transmit a variety of human pathogens acting as disseminators of the so-called vector-borne diseases. Leishmaniasis is a spectrum of diseases caused by different Leishmania species, transmitted quasi worldwide by sand flies. However, whereas many laboratories focus on the disease(s) and etiological agents, considerably less study the respective vectors. In fact, information on sand flies is neither abundant nor easy to find; aspects including basic biology, ecology, and sand-fly-Leishmania interactions are usually reported separately. Here, we compile elemental information on sand flies, in the context of leishmaniasis. We discuss the biology, distribution, and life cycle, the blood-feeding process, and the Leishmania-sand fly interactions that govern parasite transmission. Additionally, we highlight some outstanding questions that need to be answered for the complete understanding of parasite-vector-host interactions in leishmaniasis.

The Effect of curcumin on Expression of INFγ, TNF-α and iNOS Genes in PBMCs Infected with Leishmania major [MRHO/IR/75/ER].

Alinejad, S., Khademvatan, S., Amani, S., Asadi, N., Tappeh, K., Yousefi, E., Miandoabi, T.
04-04-2022
Infect Disord Drug Targets
https://doi.org/10.2174/1871526522666220404083220

Leishmaniasis, caused by Leishmania parasite, is one of the most important tropical neglected diseases. The urgent search for effective, inexpensive, and preferably herbal anti-leishmanial agents, is needed. Curcumin is a natural polyphenolic compound derived from turmeric that is well known for its antioxidant, anti-inflammatory, anti-tumor, and anti-cancer activity. The present work evaluates the anti-leishmanial [Leishmania major] activity of curcumin. The infected PBMCs were treated with curcumin. The ROS level at 6, 12, 24 h and genes expression level at 24, 48 and 72 h of PBMCs after treatment with curcumin were determined. Based on the results, the curcumin concentrations of 268 µM [24 h] and 181.2 µM [72 h] were defined as IC50 against L. major promastigotes. Treatment of L. major infected-Peripheral blood mononuclear cells [PBMCs] with IC50 concentrations of curcumin, depending on exposure time, significantly induced the reactive oxygen species [ROS] generation and increased the expression levels of interferon-gamma [IFN-γ], tumor necrosis factor-alpha [TNF-α], and nitric oxide synthase [iNOS] genes. These findings suggest the potential of curcumin against Leishmaniasis Keywords: Curcumin, Gene expression, Leishmania major, PBMCs, Tumor necrosis factor,Interferon gamma.

Bioactivity of Natural Polyphenols as Antiparasitic Agents and their Biochemical Targets.

Soto-Sánchez, J.
04-04-2022
Mini Rev Med Chem
https://doi.org/10.2174/1389557522666220404090429

Leishmaniasis and trypanosomiasis are diseases that affect public health worldwide due to their high incidence, morbidity, and mortality. Available treatments are costly, prolonged, and toxic, not to mention the problem of parasite resistance. The development of alternative treatments is justified and polyphenols show promising activity. The main aim of this mini-review was to analyze the most promising phenolic compounds with reported antileishmanial and antitrypanosomal activity as well as their mechanisms of action. We found that the mode of action of these natural compounds mainly lignans, neolignans, and flavonoids depends on the organism they act on and includes,

macrophage activation, induction of morphological changes such as chromatin condensation, DNA fragmentation, accumulation of acidocalcisomes, and glycosomes, Golgi damage and mitochondrial dysfunction as well as negative regulation of mitochondrial enzymes and other essential enzymes for parasite survival such as arginase. This gives a wide scope for future research towards the rational development of anti-kinetoplastid drugs. Although the specific molecular targets, bioavailability, route of administration, and dosages of some of these natural compounds need to be determined, polyphenols and their combinations represent a very promising and safe strategy to be considered for use against Leishmania spp and Trypanosoma spp. In addition, these compounds may provide a scaffold for developing new, more potent, and more selective antiprotozoal agents.

Correction: A spatio-temporal approach to short-term prediction of visceral leishmaniasis diagnoses in India.

PLOS NTDs Staff
04-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010346

[This corrects the article DOI: 10.1371/journal.pntd.0008422.].

Erratum for Weinkopff et al., "*Leishmania* Infection Induces Macrophage Vascular Endothelial Growth Factor A Production in an ARNT/HIF-Dependent Manner".

Weinkopff, T., Roys, H., Bowlin, A., Scott, P.
04-04-2022
Infect Immun
https://doi.org/10.1128/iai.00019-22

Nanomedicine in leishmaniasis: A promising tool for diagnosis, treatment and prevention of disease - An update overview.

Revue de littérature

Assolini, J., Machado Carloto, A., Taciane da Silva Bortoleti, B., Gonçalves, M., Pellissier, F., Feuser, P., Cordeiro, A., Hermes de Araújo, P., Sayer, C., Miranda Sapla, M., Pavanelli, W.
31-03-2022
Eur J Pharmacol
https://pubmed.ncbi.nlm.nih.gov/35367420

Leishmaniasis is a neglected tropical disease that has a wide spectrum of clinical manifestations, ranging from visceral to cutaneous, with millions of new cases and thousands of deaths notified every year. The severity of the disease and its various clinical forms are determined by the species of the causative agent, Leishmania, as well as the host's immune response. Major challenges still exist in the diagnosis and treatment of leishmaniasis, and there is no vaccine available to prevent this disease in humans. Nanotechnology has emerged as a promising tool in a variety of fields. In this review, we highlight the main and most recent advances in nanomedicine to improve the diagnosis and treatment, as well as for the development of vaccines, for leishmaniasis. Nanomaterials are nanometric in size and can be produced by a variety of materials, including lipids, polymers, ceramics, and metals, with varying structures and morphologies. Nanotechnology can be used as biosensors to detect antibodies or antigens, thus improving the sensitivity and specificity of such immunological and molecular diagnostic tests. While in treatment, nanomaterials can act as drug carriers or, be used directly, to reduce any toxic effects of drug compounds to the host and to be more selective towards the parasite. Furthermore, preclinical studies show that different nanomaterials can carry different Leishmania antigens, or even act as adjuvants to improve a Th1 immune response in an attempt to produce an effective vaccine.

miRNAs in the regulation of mTOR signaling and host immune responses: the case of Leishmania infections.

Revue de littérature

Rashidi, S., Mansouri, R., Ali-Hassanzadeh, M., Ghani, E., Karimazar, M., Muro, A., Nguewa, P., Manzano-Román, R.
31-03-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35367408

Micro RNAs (miRNAs), as regulators of gene expression at the post-transcriptional level, can respond to/or interact with cell signaling and affect the pathogenesis of different diseases/infections. The interaction/crosstalk of miRNAs with various cellular signaling networks including mTOR (as a master regulator of signaling relevant to different cellular mechanisms) might lead to the initiation, progression or restriction of certain disease processes. There are numerous studies that have identified the crosstalk between regulatory miRNA expression and the mTOR pathway (or mTOR signaling regulated by miRNAs) in different diseases which has a dual function in pathogenesis. However, the corresponding information in parasitic infections remains scarce. miRNAs have been suggested as specific targets for therapeutic strategies in several disorders such as parasitic infections. Thus, the targeting of miRNAs (as the modulators/regulators of mTOR) by small molecules and RNA-based therapeutics and consequently managing and modulating mTOR signaling and the downstream/related cell signaling/pathways might shed some light on the design of new therapeutic strategies against parasitic diseases, including Leishmaniasis. Accordingly, the present study attempts to highlight the importance of the crosstalk between regulatory miRNAs and mTOR signaling, and to review the relevant insights into parasitic infections by focusing specifically on Leishmania.

Ruthenium metallotherapeutics: novel approaches to combatting parasitic infections.

Britten, N., Butler, J.
01-04-2022

Curr Med Chem
https://doi.org/10.2174/0929867329666220401105444

Human parasitic infections cause a combined global mortality rate of over one million people per annum and represent some of the most challenging diseases for medical intervention. Current chemotherapeutic strategies often require prolonged treatment, coupled with subsequent drug-induced cytotoxic morbidity to the host, while resistance generation is also a major concern. Metals have been used extensively throughout the history of medicine, with more recent applications as anticancer and antimicrobial agents. Ruthenium metallotherapeutic antiparasitic agents are highly effective at targeting a range of key parasites, including the causative agents of malaria, trypanosomiasis, leishmaniasis, amoebiasis, toxoplasmosis and other orphan diseases, while demonstrating lower cytotoxicity profiles than current treatment strategies. Generally, such compounds also demonstrate activity against multiple cellular target sites within parasites, including inhibition of enzyme function, cell membrane perturbation, and alterations to metabolic pathways, therefore reducing the opportunity for resistance generation. This review provides a comprehensive and subjective analysis of the rapidly developing area of ruthenium metal-based antiparasitic chemotherapeutics, in the context of rational drug design and potential clinical approaches to combatting human parasitic infections.

Probing the Interactions Responsible for the Structural Stability of Trypanothione Reductase Through Computer Simulation and Biophysical Characterization.

Kumar, A., Nimsarkar, P., Singh, S.
02-04-2022
Protein J
https://doi.org/10.1007/s10930-022-10052-x

With the necessity to develop antileishmanial drugs with substrate specificity, trypanothione reductase (TryR) has gained popularity in parasitology. TryR is unique to be present only in trypanosomatids and is functionally similar to glutathione in mammals. It protects against oxidative stress exerted by the host defense mechanism. The TryR enzyme is essential for the survival of Leishmania parasites in the host as it reduces trypanothione and aids in neutralizing hydrogen peroxide produced by the host macrophages during infection. Henceforth, it becomes vital to decipher their functional stability and behaviour in the presence of denaturants. Our study is focused on structural, functional and behavioural stability aspects of TryR with different concentrations of Urea, Guanidinium chloride, alcohol based compounds followed by extensive molecular dynamics simulations in a lipid bilayer system. The results obtained from the study reveal an interesting insight into the possible mechanisms of modulation of the structure, function and stability of the TryR protein.

Hexane extracts from fruit of two varieties of *Capsicum chinense* Jacq.: their volatile constituents and antiacetylcholinesterase, antileishmanial and antiproliferative activities.

Toigo, S., Fernandes, C., Squarisi, I., Ribeiro, A., Tavares, D., Candido, A., Magalhães, L., Moreira, F., Crotti, A., Miranda, M.
31-03-2022
Nat Prod Res
https://doi.org/10.1080/14786419.2022.2057972

This article aims to investigate volatile constituents and antiacetylcholinesterase, antileishmanial and antiproliferative activities of hexane extracts from *Capsicum chinense* fruit (unripe bode pepper 'HE-UB' and ripe little beak pepper 'HE-RB'). HE-UB and HE-RB were screened by the microplate assay method to determine their antiacetylcholinesterase activity. Both exhibited inhibitory potential, i. e., IC_{50} = 41.5 and 20.3 µg/mL, respectively. HE-UB (IC_{50} = 67.19 µg/mL) and HE-RB (IC_{50} = 38.16 µg/mL) exhibited antileishmanial activity against promastigote forms of *Leishmania (Leishmania) amazonensis*. In addition, HE-UB and HE-RB demonstrated cytotoxic activity against different human tumor cell lines with IC_{50} ranging from 325.40 to 425.0 µg/mL. Both GC-FID and GC-MS analyses revealed that the major component in both extracts was *E*-caryophyllene. In short, HE-RB was more satisfactory than HE-UB in all *in vitro* activities under evaluation. These findings may be used as initial data for further studies of *Capsicum* species.

Exposure to Phlebotomus perniciosus sandfly vectors is positively associated with Toscana virus and Leishmania infantum infection in human blood donors in Murcia Region, southeast Spain.

Ortuño, M., Muñoz, C., Spitzová, T., Sumova, P., Iborra, M., Pérez-Cutillas, P., Ayhan, N., Charrel, R., Volf, P., Berriatua, E.
31-03-2022
Transbound Emerg Dis
https://doi.org/10.1111/tbed.14520

Antibodies against Phlebotomus perniciosus sandfly salivary gland homogenate (SGH) and recombinant protein rSP03B, sandfly-borne Toscana virus (TOSV), Sandfly Fever Sicilian virus (SFSV) and Leishmania, as well as DNA of the latter parasite, were investigated in 670 blood samples from 575 human donors in Murcia Region, southeast Spain, in 2017 and 2018. The estimated SGH and rSP03B seroprevalences were 69% and 88%, respectively, although correlation between test results was relatively low (ρ = 0.39). Similarly, TOSV, SFSV and Leishmania seroprevalences were 26%, 0% and 1%, respectively, and Leishmania PCR prevalence was 2%. Prevalences were significantly greater in 2017, overdispersed and not spatially related to each other although both were positively associated with SGH but not to rSP03B antibody optical densities, questioning the value of the latter as a diagnostic marker for these infections in humans.

Transcriptomic Analysis in Human Macrophages Infected with Therapeutic Failure Clinical Isolates of *Leishmania infantum*.

Perea-Martínez, A., García-Hernández, R., Manzano, J., Gamarro, F.
30-03-2022
ACS Infect Dis
https://doi.org/10.1021/acsinfecdis.1c00513

Leishmaniasis is one of the neglected tropical diseases with a worldwide distribution, affecting humans and animals. In the absence of an effective vaccine, current treatment is through the use of chemotherapy; however, existing treatments have frequent appearance of drug resistance and therapeutic failure (TF). The identification of factors that contribute to TF in leishmaniasis will provide the basis for a future therapeutic strategy more efficient for the control of this disease. In this article, we have evaluated the transcriptomic changes in the host cells THP-1 after infection with clinical *Leishmania infantum* isolates from leishmaniasis patients with TF. Our results show that distinct *L. infantum* isolates differentially modulate host cell response, inducing phenotypic changes that probably may account for parasite survival and TF of patients. Analysis of differential expression genes (DEGs), with a statistical significance threshold of a fold change ≥ 2 and a false discovery rate value ≤ 0.05, revealed a different number of DEGs according to the *Leishmania*line. Globally, there was a similar number of genes up- and downregulated in all the infected host THP-1 cells, with exception of Hi-L2221, which showed a higher number of downregulated DEGs. We observed a total of 58 DEGs commonly modulated in all infected host cells, including upregulated ($log_2FC \geq 1$) and downregulated ($log_2FC \leq -1$) genes. Based on the results obtained from the analysis of RNA-seq, volcano plot, and GO enrichment analysis, we identified the most significant transcripts of relevance for their possible contribution to the TF observed in patients with leishmaniasis.

Natural compounds based chemotherapeutic against Chagas disease and leishmaniasis: mitochondrion as a strategic target.

Lazarin-Bidóia, D., Garcia, F., Ueda-Nakamura, T., Silva, S., Nakamura, C.
30-03-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35352776

Over the past years, natural products have been explored in order to find biological active substances to treat various diseases. Regarding their potential action against parasites such as trypanosomatids, specially Trypanosoma cruzi and Leishmania spp., much advance has been achieved. Extracts and purified molecules of several species from genera Piper, Tanacetum, Porophyllum, and Copaifera have been widely investigated by our research group and exhibited interesting antitrypanosomal and antileishmanial activities. These natural compounds affected different structures in parasites, and we believe that the mitochondrion is a strategic target to induce parasite death. Considering that these trypanosomatids have a unique mitochondrion, this cellular target has been extensively studied aiming to find more selective drugs, since the current treatment of these neglected tropical diseases has some challenges such as high toxicity and prolonged treatment time. Here, we summarise some results obtained with natural products from our research group and we further highlighted some strategies that must be considered to finally develop an effective chemotherapeutic agent against these parasites.

A Review on Climate, Air Pollution, and Health in North Africa.

Revue de littérature

Imane, S., Oumaima, B., Kenza, K., Laila, I., Youssef, E., Zineb, S., Mohamed, E.
30-03-2022
Curr Environ Health Rep
https://doi.org/10.1007/s40572-022-00350-y

The aim of this review is to summarize and provide clear insights into studies that evaluate the interaction between air pollution, climate, and health in North Africa. Few studies have estimated the effects of climate and air pollution on health in North Africa. Most of the studies highlighted the evidence of the link between climate and air pollution as driving factors and increased mortality and morbidity as health outcomes. Each North African country prioritized research on a specific health factor. It was observed that the health outcome from each driving factor depends on the studied area and data availability. The latter is a major challenge in the region. As such, more studies should be led in the future to cover more areas in North Africa and when more data are available. Data availability will help to explore the applicability of different tools and techniques new to the region. This review explores studies related to climate and air pollution, and their possible impacts on health in North Africa. On one hand, air quality studies have focused mainly on particulate matter exceedance levels and their long-term exposure impacts, namely, morbidity and mortality. The observed differences between the various studies are mainly due to the used exposure-response function, the studied population, background emissions, and natural emission from the Sahara Desert that characterize the region. On the other hand, climate studies have focused primarily on the impact of heat waves, vector-borne disease, and mental disorders. More than half of these studies have been on leishmaniasis disease. The review revealed unbalanced and insufficient research on health impacts from air pollution episodes and climate extremes across the region.

Leishmaniose cutanée observée chez une jeune fille de 12 ans récemment immigrée de Syrie

Alghounaim, M., Chivinski, J., Barkati, S.
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CMAJ
https://doi.org/10.1503/cmaj.210847-f

Appearances are deceiving: immature lymphocytes in Leishmaniasis.

Galiacho, V., Pomposo, M., Echebarria-Barona, A., Urdiales, P., Ruiz, J.

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Blood Res

https://doi.org/10.5045/br.2022.2021191

Somalia tackles leprosy and visceral leishmaniasis.

Bagcchi, S.

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Lancet Infect Dis

https://pubmed.ncbi.nlm.nih.gov/35338873

TDP1 knockout Leishmania donovani accumulate topoisomerase 1-linked DNA damage and are hypersensitive to clinically used antileishmanial drugs.

Chowdhury, S., Das, S., Banerjee, B., Paul Chowdhuri, S., Majumder, H., Das, B.

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FASEB J

https://doi.org/10.1096/fj.202101668RR

Leishmania donovani, a unicellular protozoan parasite, causes a wide range of human diseases including fatal visceral leishmaniasis. Tyrosyl DNA-phosphodiesterase 1 (TDP1) hydrolyzes the phosphodiester bond between DNA 3'-end and a tyrosyl moiety of trapped topoisomerase I-DNA covalent complexes (Top1cc). We have previously shown Leishmania harbors a TDP1 gene (LdTDP1), however, the biological role of TDP1 remains largely unknown. In the present study, we have generated TDP1 knockout L. donovani (LdTDP1$^{-/-}$) promastigotes and have shown that LdTDP1$^{-/-}$ parasites are deficient in 3'-phosphodiesterase activities and were hypersensitive to Top1-poison like camptothecin (CPT), DNA alkylation agent like methyl methanesulfonate, and oxidative DNA lesions generated by hydrogen peroxide but were not sensitive to etoposide. We also detected elevated levels of CPT-induced reactive oxygen species triggering cell cycle arrest and cell death in LdTDP1$^{-/-}$ promastigotes. LdTDP1$^{-/-}$ promastigotes accumulate a significant change in the membrane morphology with the accumulation of membrane pores, which is associated with oxidative stress and lipid peroxidation. To our surprise, we detected that LdTDP1$^{-/-}$ parasites were hypersensitive to antileishmanial drugs like amphotericin B and miltefosine, which could be rescued by complementation of wild-type TDP1 gene in the LdTDP1$^{-/-}$ parasites. Notably, multidrug-resistant L. donovani clinical isolates showed a marked reduction in TDP1 expression and were sensitive to Top1 poisons. Taken together, our study provides a new role of LdTDP1 in protecting L. donovani parasites from oxidative stress-induced DNA damage and resistance to amphotericin B and miltefosine.

Autochthonous Leishmania infantum in Dogs, Zambia, 2021.

Squarre, D., Chambaro, H., Hayashida, K., Moonga, L., Qiu, Y., Goto, Y., Oparaocha, E., Mumba, C., Muleya, W., Bwalya, P., Chizimu, J., Chembensofu, M., Simulundu, E., Mwasinga, W., Banda, N., Mwenda, R., Yamagishi, J., Nalubamba, K., Banda, F., Munyeme, M., Sawa, H., Fandamu, P.

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Emerg Infect Dis

https://doi.org/10.3201/eid2804.212378

Leishmaniases are neglected tropical diseases of humans and animals. We detected Leishmania infantum in 3 mixed-breed dogs in Zambia that had no travel history outside the country. Our findings suggest presence of and probable emergence of leishmaniasis in Zambia, indicating the need for physicians and veterinarians to consider the disease during diagnosis.

A dataset of proteins associated with *Trypanosoma cruzi LYT1* mRNAs.

Márvez, E., Segura, C., Requena, J., Puerta, C.

15-02-2022

Data Brief

https://doi.org/10.1016/j.dib.2022.107953

Post-transcriptional gene regulation in *Trypanosoma cruzi*, the etiological agent of Chagas disease, plays a critical role in ensuring that the parasite successfully completes its life cycle in both of its obligate hosts: insect vector and mammals. This regulation is basically governed by RNA binding proteins (RBPs) through their interactions with *cis*-elements located in the UTRs of their mRNA targets. LYT1 gene, coding for a virulence factor of *T. cruzi*, is expressed into two isoforms: kLYT1 and mLYT1, which play different functions according to their cellular location and parasite life-cycle stages. Whereas kLYT1 exhibits a regulatory role during the epimastigote-to-metacyclic trypomastigote stage transition, mLYT1 acts as a pore-forming protein, relevant for host cell invasion and parasite intracellular survival. Considering the LYT1 biological relevance and the fact that this is a protein exclusive of *T. cruzi*, the protein and its mechanisms regulating the alternative gene expression products are promising targets for therapeutic intervention. In this work, an experimental approach consisting of pull-downs assays followed by proteomic analyzes was carried out to identify the proteins interacting with the different LYT1 mRNAs. The dataset presented here was obtained through three biological replicates using all the different UTRs characterized in the LYT1 mRNAs (i.e., 5´UTR kLYT1, 5´UTR mLYT1, and I and II-type 3´UTRs) as baits, and protein extracts from epimastigotes and trypomastigotes of the 058 PUJ (DTU I) strain. Bound proteins were analyzed by liquid chromatography coupled to mass spectrometry (LC/MS). As a control of non-specificity, the same protein extracts were incubated with *Leishmania braziliensis* rRNA and the bound proteins also identified by LC/MS. In all, 1,557 proteins were identified, 313 of them were found in at least two replicates and 18 proteins were exclusively associated with the LYT1 baits. Of these, six

proteins have motifs related to RNA binding, and seven remain annotated as hypothetical proteins. Remarkably, three of these hypothetical proteins also contain nucleic acid binding motifs. This knowledge, beside expanding the known *T. cruzi* proteome, gains insight into putative regulatory proteins responsible for alternative LYT1 mRNAs processing. Raw mass spectrometry data are available via MassIVE proteome Xchange with identifier PXD027371.

Xanthinuria secondary to allopurinol treatment in dogs with leishmaniosis: Current perspectives of the Iberian veterinary community.

Jesus, L., Arenas, C., Domínguez-Ruiz, M., Silvestrini, P., Englar, R., Roura, X., Leal, R.
24-02-2022
Comp Immunol Microbiol Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35240487

Xanthinuria is a significant adverse effect in dogs on long-term allopurinol for treatment of leishmaniosis. The study aims to investigate how the Iberian veterinary community (IVC) identifies, manages, and proactively prevents xanthinuria secondary to allopurinol treatment. A cross-sectional study was conducted using an online survey, translated into two languages, and disseminated to the IVC via social networking forums. Respondents were asked to share their treatment regimens, adverse effects attributed to treatment, as well as preventive and reactive measures against xanthuria. Of two-hundred and thirty respondents, 99.6% prescribe allopurinol for canine leishmaniosis. Xanthinuria was estimated to happen in less than one out of every four dogs by 91.7% of the clinicians. Xanthinuria has been detected by 71.6% of respondents at least once. Three out of every four respondents inform owners about deleterious effects of allopurinol, and 28.4% consider implementing a change in diet in advance of treatment as a proactive measure. To monitor xanthinuria, urinalysis and diagnostic imaging are used by 71.2% and 31% of clinicians respectively. When xanthinuria is detected, 43.2% of the respondents discontinue allopurinol, 24% replace it by nucleotide-analogs, 14.9% reduce its dosage, and 3.1% split its dosage but increase administration frequency. Additional measures are taken by 72.1% of the respondents, 59.4% of whom prescribe a low-purine diet. The IVC recognizes xanthinuria as a fairly common secondary effect of long-term allopurinol treatment in dogs with leishmaniosis and recommends periodically monitoring and preventive measures.

Erratum: First-in-class pyrido[2,3-d]pyrimidine-2,4(1H,3H)-diones against leishmaniasis and tuberculosis: Rationale, in vitro, ex vivo studies and mechanistic insights.

Ramesh, D., Sarkar, D., Joji, A., Singh, M., Mohanty, A., Vijayakumar, B., Chatterjee, M., Sriram, D., Muthuvel, S., Kannan, T.
01-03-2022
Arch Pharm (Weinheim)
https://doi.org/10.1002/ardp.202270007

Treatment of Cutaneous Leishmaniasis and Insights into Species-Specific Responses: A Narrative Review.

Revue de littérature

Madusanka, R., Silva, H., Karunaweera, N.
22-02-2022
Infect Dis Ther
https://doi.org/10.1007/s40121-022-00602-2

Cutaneous leishmaniasis (CL) is a complex skin infection that has imposed a heavy burden on many developing countries and is caused by more than 20 Leishmania species. This disease is predominantly associated with disfiguring scars and major social stigma upon infection. The severity of the disease seemingly depends on many factors including the species of parasite, the host, region of endemicity, socio-economic status and the accessibility to health facilities. Despite myriad studies that have been performed on current and novel therapies, the treatment outcomes of CL remain contentious, possibly because of the knowledge gaps that still exist. The differential responses to the current CL therapies have become a major drawback in disease control, and the dearth of information on critical analyses of outcomes of such studies is a hindrance to the overall understanding. On the basis of currently available literature on treatment outcomes, we discuss the most effective doses, drug susceptibilities/resistance and treatment failures of the Leishmania genus for both monotherapy and combination therapy. This review focuses on the available treatment modalities for CL caused by different Leishmania species, with insights into their species-specific efficacies, which would inform the selection of appropriate drugs for the treatment and control of leishmaniasis.

Sex under pressure: stress facilitates Leishmania in vitro hybridization.

Monte-Neto, R., Fernandez-Prada, C., Moretti, N.
16-02-2022
Trends Parasitol
https://pubmed.ncbi.nlm.nih.gov/35181250

The selection of Leishmania hybrids in axenic culture was considered rare until recently, when Louradour and Ferreira et al., demonstrated that induced DNA damage facilitates genetic exchange, resulting in full genome tetraploid progenies in vitro. Meiosis-related gene homologues HAP2, GEX1, and RAD51 were found to be involved, opening new avenues for functional genomic studies.

Correction to: Update of the Phlebotominae Fauna with New Records for Argentina and Observations on Leishmaniasis Transmission Scenarios at a Regional Scale.

Moya, S., Szelag, E., Manteca-Acosta, M., Quintana, M., Salomón, O.
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Neotrop Entomol
https://doi.org/10.1007/s13744-022-00941-2

Fabrication data of two light-responsive systems to release an antileishmanial drug activated by infrared photothermal heating.

Vitorino, L., Dos Santos, T., Bessa, I., Santos, E., Verçoza, B., de Oliveira, L., Rodrigues, J., Ronconi, C.
19-01-2022
Data Brief
https://doi.org/10.1016/j.dib.2022.107841

The data provided in this study are related to the fabrication of two light-responsive systems based on reduced graphene oxide (rGO) functionalized with the polymers Pluronic P123 (P123), rGO-P123, and polyethyleneimine (PEI), rGO-PEI, and loaded with amphotericin B (AmB), an antileishmanial drug. Here are described the experimental design to obtain the systems and characterization methods, such as Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy (ATR-FTIR), Raman Spectroscopy, Powder X-Ray Diffraction, Transmission Electron Microscopy, Scanning Electron Microscopy and Thermogravimetric Analyses. Also, AmB spectroscopy studies are described. The materials rGO-P123 and rGO-PEI were loaded with AmB and the optimization of AmB and polymer fragments structures revealed several possible hydrogen bonds formed between the materials and the drug. The drug release was analyzed with and without Near-Infrared (NIR) light. In the studies conducted under NIR light irradiation for 10 min, an infrared lamp was disposed at 64 cm from the samples and an optical fiber thermometer was employed to measure the temperature variation. Cytotoxicity studies and antiproliferative assays against *Leishmania amazonensis* promastigotes were evaluated. The complete work data entitled Amphotericin-B-Loaded Polymer-Functionalized Reduced Graphene Oxides for *Leishmania amazonensis* Chemo-Photothermal Therapy have been published to Colloids and Surfaces B: Bionterfaces (https://doi.org/10.1016/j.colsurfb.2021.112169) [1].

Synthesis and characterization of zinc derivatized 3, 5-dihydroxy 4', 7-dimethoxyflavone and its anti leishmaniasis activity against Leishmania donovani.

Gupta, M., Chiranjivi, A., Dutta, T., Dubey, V., Rangan, L.
10-02-2022
Biometals
https://doi.org/10.1007/s10534-022-00364-x

This study reports the synthesis and characterization of zinc derivatized 3,5-dihydroxy 4', 7- dimethoxyflavone (DHDM-Zn) compound for the development of new antileishmanial agents. The interaction studies of DHDM with zinc were carried out by UV spectra and fluorescence spectra analysis. Characterization of the complex was further accomplished by multi-spectroscopic techniques such as FTIR, Raman, HRMS, NMR, FESEM-EDX. The morphological and topographical studies of synthesized DHDM-Zn were carried out using FESEM with EDX. Further, it was demonstrated that DHDM-Zn exhibited an excellent in vitro antagonistic effect against the promastigote form of L. donovani. In addition, the possible mechanisms of promastigote L. donovani cell death, by involvement of derivatized compound in arrest of the cell cycle in the G1 phase and residual cell count reduction were investigated. Promastigote growth kinetics performed in the presence of the derivatized compound revealed a slow growth rate. The combination of growth kinetics and cell cycle analysis, made it possible to interpret and classify the cause of leishmanial cell death accurately. These results support that zinc derivatized complex (DHDM-Zn) might work as a lead compound for designing and developing a new antileishmanial drug.

Phenotypic investigation of 4-nitrophenylacetyl- and 4-nitro-1*H*-imidazoyl-based compounds as antileishmanial agents.

Santos, C., Zhang, H., Batista, M., de Oliveira, G., Demarque, K., da Silva, N., Moreira, O., Ogungbe, I., Soeiro, M.
03-02-2022
Parasitology
https://doi.org/10.1017/S0031182021002079

Cutaneous leishmaniasis (CL) is a spectrum of clinical manifestations characterized by severe skin ulcerations that leads to social stigma. There are limited treatment options for CL, and the available drugs are becoming less efficacious due to drug resistance. More efficacious and safer antileishmanial drugs are needed. In this study, the biological effect of seven synthetically accessible nitroaromatic compounds was evaluated in vitro against amastigotes of Leishmania amazonensis, followed by in vivo evaluation using mouse models of CL. Two compounds (6 and 7) were active against amastigotes in vitro [half-maximal effective concentration (EC50): 4.57 ± 0.08 and 9.19 ± 0.68 µm, respectively], with selectivity indexes >50, and the other compounds were not selective. In vivo, compounds 6 and 7 (10 mg kg−1, twice a day for 14 days) failed to reduce skin lesion sizes and parasite loads determined by light microscopy of lesion imprints and quantitative polymerase chain reaction. Nevertheless, the in vitro leishmanicidal efficacy sustained their use as templates for nitroimidazole-based antileishmanial drug discovery programmes focusing on analogues with more suitable properties.

First-in-class pyrido[2,3-d]pyrimidine-2,4(1H,3H)-diones against leishmaniasis and tuberculosis: Rationale, in vitro, ex vivo studies and mechanistic insights.

Ramesh, D., Sarkar, D., Joji, A., Singh, M., Mohanty, A., G Vijayakumar, B., Chatterjee, M., Sriram, D., Muthuvel, S., Kannan, T.
01-02-2022

Arch Pharm (Weinheim)
https://doi.org/10.1002/ardp.202100440

Pyrido[2,3-d]pyrimidine-2,4(1H,3H)-diones were synthesized, for the first time, from indole chalcones and 6-aminouracil, and their ability to inhibit leishmaniasis and tuberculosis (Tb) infections was evaluated. The in vitro antileishmanial activity against promastigotes of Leishmania donovani revealed exceptional activities of compounds 3, 12 and 13, with IC_{50} values ranging from 10.23±1.50 to 15.58±1.67μg/ml, which is better than the IC_{50} value of the standard drug pentostam of 500μg/ml. The selectivity of the compounds towards Leishmania parasites was evaluated via ex vivo studies in Swiss albino mice. The efficiency of these compounds against Tb infection was then evaluated using the in vitro anti-Tb microplate Alamar Blue assay. Five compounds, 3, 7, 8, 9 and 12, showed MIC_{100} values against the Mycobacterium tuberculosis H_{37} Rv strain at 25μg/ml, and compound 20 yielded an MIC_{100} value of 50μg/ml. Molecular modelling of these compounds highlighted interactions with binding sites of dihydrofolate reductase, pteridine reductase and thymidylate kinase, thus establishing the rationale of their pharmacological activity against both pathogens, which is consistent with the in vitro results. From the above results, it is clear that compounds 3 and 12 are promising lead candidates for Leishmania and Mycobacterium infections and may be promising for coinfections.

Topical treatment of cutaneous leishmaniasis lesions using quercetin/ Artemisia-capped silver nanoparticles ointment: Modulation of inflammatory response.

Alemzadeh, E., Karamian, M., Abedi, F., Hanafi-Bojd, M.
28-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35093324

Leishmaniasis is a major health issue that affects people all over the world, producing considerable morbidity and mortality in Asia, Africa, and the Americas, and existing treatments have significant side effects. Nowadays, the development of nanoscale materials such as biogenic silver nanoparticles has attracted much medical attraction. In this study, AgNPs were synthesized from leaf extract of Artemisia aucheri. Biosynthesized AgNPs were analyzed by UV-visible spectroscopy, dynamic light scattering and zeta potential, fourier transform infrared spectroscopy and field emission scanning electron microscopy. Biosynthesized AgNPs were examined for anti-leishmanial and antibacterial activity. The in vivo study was conducted by treating the L. major infected BALB/c mice with quercetin/ artemisia-capped silver nanoparticles ointment topically for 21 consecutive days. The in vitro and in vivo results showed that the ointment containig quercetin/artemisia-capped silver nanoparticles have the potential to decrease inflammatory responses and enhance wound healing with granulation tissue formation compared to the untreated group. Therefore, biogenic nanoparticles are safe, eco-friendly, and easy to synthesize and could be considered as an alternative regimen for treatment of L. major.

Effect of topical berberine in murine cutaneous leishmaniasis lesions.

Calvo, A., Moreno, E., Aldalur, I., Sanmartín, C., Larrea, E., González-Peñas, E., Irache, J., Espuelas, S.
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J Antimicrob Chemother
https://doi.org/10.1093/jac/dkac007

More effective topical treatments remain an unmet need for the localized forms of cutaneous leishmaniasis (CL). The aim of this study was to evaluate the efficacy and safety of a topical berberine cream in BALB/c mice infected with Leishmania major parasites. A cream containing 0.5% berberine-β-glycerophosphate salt and 2.5% menthol was prepared. Its physicochemical and stability properties were determined. The cream was evaluated for its capacity to reduce lesion size and parasitic load as well as to promote wound healing after twice-a-day administration for 35 days. Clinical biochemical profile was used for estimating off-target effects. In vitro time-to-kill curves in L. major-infected macrophages and skin and plasma pharmacokinetics were determined, aiming to establish pharmacokinetic/pharmacodynamic relationships. The cream was stable at 40°C for 3 months and at 4°C for at least 8 months. It was able to halt lesion progression in all treated mice. At the end of treatment, parasite load in the skin was reduced by 99.9% (4 log) and genes involved in the wound healing process were up-regulated compared with untreated mice.The observed effects were higher than expected from in vitro time-to-kill kinetic and plasma berberine concentrations, which ranged between 0.07 and 0.22 μM. The twice-a-day administration of a topical berberine cream was safe, able to stop parasite progression and improved the appearance of skin CL lesions. The relationship between drug plasma levels and in vivo effect was unclear.

Leishmania diversity in bats from an endemic area for visceral and cutaneous leishmaniasis in Southeastern Brazil.

Vieira, T., Silva, S., Lima, L., Sabino-Santos, G., Duarte, E., Lima, S., Pereira, A., Ferreira, F., de Araújo, W., Teixeira, M., Ursine, R., Gontijo, C., Melo, M.
24-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35085511

This study aimed to determine the occurrence of Leishmania infection in bats in urban and wild areas in an endemic municipality for visceral and cutaneous leishmaniasis in Minas Gerais, Brazil. Between April 2014 to April 2015, 247 bats were captured and classified into 26 species belonging to Phyllostomidae (90.7%), Vespertilionidae (8.1%) and Molossidae (1.2%) families. Blood samples from 247 bats were collected and submitted to nested-PCR, targeting the variable

V7-V8 region of the SSU rRNA gene, followed by sequencing of the PCR product. The overall infection rate of Leishmania spp. in bats was 4.4%. Of the eleven bats infected, ten were frugivorous bats: Artibeus planirostris (8/11), Artibeus lituratus (1/11) and Artibeus cinereus (1/11) and one a nectarivorous bat (Glossophaga soricina). None of the individuals exhibited macroscopic alterations in the skin, spleen or liver. Phylogenetic analysis separated Leishmania species in clades corresponding to the subgenera Viannia, Leishmania, and Mundinia, and supported that the isolates characterized in the present study clustered closely with Leishmania (Viannia) sp., Leishmania (Leishmania) infantum and Leishmania (Leishmania) amazonensis. Here we report for the first time the bat Artibeus cinereus as a host of Leishmania (Leishmania) amazonensis. In the study we found that the mean abundance of bats did not differ in wild habitats and urban areas and that bat-parasite interactions were similarly distributed in the two environments. On the other hand, further studies should be conducted in more recent times to verify whether there have been changes in these parameters.

Antileishmanial activity and insights into the mechanisms of action of symmetric Au(I) benzyl and aryl-N-heterocyclic carbenes.

Rosa, L., Galuppo, C., Lima, R., Fontes, J., Siqueira, F., Júdice, W., Abbehausen, C., Miguel, D.
15-01-2022
J Inorg Biochem
https://pubmed.ncbi.nlm.nih.gov/35065320

Leishmania amazonensis and L. braziliensis are the main etiological agents of the American Tegumentary Leishmaniasis (ATL). Taking into account the limited effectiveness and high toxicity of the current drug arsenal to treat ATL, novel options are urgently needed. Inspired by the fact that gold-based compounds are promising candidates for antileishmanial drugs, we studied the biological action of a systematic series of six (1)-(6) symmetric Au(I) benzyl and aryl-N-heterocyclic carbenes. All compounds were active at low micromolar concentrations with 50% effective concentrations ranging from 1.57 to 8.30 µM against Leishmania promastigotes. The mesityl derivative (3) proved to be the best candidate from this series, with a selectivity index ~13 against both species. The results suggest an effect of the steric and electronic parameters of the N-substituent in the activity. Intracellular infections were drastically reduced after 24h of (2)-(5) incubation in terms of infection rate and amastigote burden. Further investigations showed that our compounds induced significant parasites' morphological alterations and membrane permeability. Also, (3) and (6) were able to reduce the residual activity of three Leishmania recombinant cysteine proteases, known as possible targets for Au(I) complexes. Our promising results open the possibility of exploring gold complexes as leishmanicidal molecules to be further screened in in vivo models of infection.

Identification of factors involved in ribosome assembly in the protozoan parasite Leishmania major.

Nepomuceno-Mejía, T., Florencio-Martínez, L., Pineda-García, I., Martínez-Calvillo, S.
15-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35041807

Formation of the ribosome subunits is a complex and progressive cellular process that requires a plethora of non-ribosomal transient proteins and diverse small nucleolar RNAs, which are involved from the synthesis of the precursor ribosomal RNA in the nucleolus to the final ribosome processing steps in the cytoplasm. Employing PTP-tagged Nop56 as a fishing bait to capture pre-ribosomal particles by tandem affinity purifications, mass spectrometry assays and a robust in silico analysis, here we describe tens of ribosome assembly factors involved in the synthesis of both ribosomal subunits in the human pathogen Leishmania major, where the knowledge about ribosomal biogenesis is scarce. We identified a large number of proteins that participate in most stages of ribosome biogenesis in yeast and mammals. Among them, we found several putative orthologs of factors not previously identified in L. major, such as t-Utp4, t-Utp5, Rrp7, Nop9 and Nop15. Even more interesting is the fact that we identified several novel candidates that could participate in the assembly of the atypical 60S subunit in L. major, which contains eight different rRNA species. As these proteins do not seem to have a human counterpart, they have potential as targets for novel anti-leishmanial drugs. Also, numerous proteins whose function is not apparently linked to ribosome assembly were copurified, suggesting that the L. major nucleolus is a multifunctional nuclear body.

Antileishmanial potential of species from the family Lamiaceae: chemical and biological aspects of non-volatile compounds.

Revue de littérature

Maciel, M., Reis, A., Fidelis, Q.
12-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35032468

Leishmaniasis is a neglected tropical disease present in more than 90 countries and annually affects about 1 million people worldwide. It is caused by the genus Leishmania protozoa that are transmitted to humans by insect bites. This disease is a serious public health problem, which can cause death, disability, and mutilation. The drugs used in treatment have high toxicity, low efficiency, high costs, and possible antiparasitic resistance. Medicinal plant-based treatments have been used for leishmaniasis by population from endemic areas. Among the main botanical families used against leishmaniasis, in different parts of the world, the family Lamiaceae stands out. In this review, the antileishmanial activity of extracts, fractions, and non-volatile compounds of Lamiaceae species are presented. Leishmania species present

in the Old and New World were evaluated and discussed. Altogether there are forty-two Lamiaceae species, belonging to twenty-six genera, and ninety-one constituents, isolated from eighteen species of this family, verified in antileishmanial assays. Chemical and biological aspects of extracts, fractions and non-volatile constituents are discussed in order to define a profile of antileishmanial plants of this family, based on the antileishmanial activities results. Notes are presented to guide future investigations to expand chemical and biological knowledge of Lamiaceae species and highlight its most promising antileishmanial agents.

Effects of multiple feedings on sensitized rabbits on the fitness of Phlebotomus papatasi (Diptera: Psychodidae).

Trimèche, M., Boussoffara, T., Chelbi, I., Cherni, S., Zhioua, S., Msallem, N., Labidi, I., Zhioua, E.
10-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35021103

In the present study, we evaluated the effects of antibodies anti-sandfly saliva on the fecundity of Phlebotomus papatasi, vector of zoonotic cutaneous leishmaniasis in the Old World. Rabbits were repeatedly exposed to sandfly bites. Immune sera showed increased levels of anti-sandfly saliva antibody compared to the pre-exposition period. The analysis of biological parameters revealed no decline on the feeding success of females P. papatasi fed on rabbits repeatedly exposed to sandfly bites. Our results showed that anti-sandfly saliva antibodies of rabbits are not detrimental to the fitness of females P. papatasi. Thus, rabbits did not acquire resistance to sandflies following repeated exposures, and that contribute in maintaining a high density of P. papatasi. To control sandfly infestations and Leishmania transmission, more studies are needed for a better understanding of the mechanisms governing the resistance of hosts to bites of sandflies.

Impact of vector control actions in the abundance of Lutzomyia longipalpis in Montes Claros, Brazil.

Rocha, M., Michalsky, É., Lara-Silva, F., Pereira, N., Lana, R., França-Silva, J., Pinheiro, L., Marinho, S., Santos, R., Santo, L., Fortes-Dias, C., Dias, E.
07-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/34998997

Visceral leishmaniasis (VL) is endemic to many states in Brazil. To prevent further expansion of the disease, the Brazilian Ministry of Health adopted integrated measures through the Program of Surveillance and Control of Visceral Leishmaniasis (PSCVL), whose actions include the diagnosis and euthanasia of seropositive dogs (the main domestic reservoirs), the use of residual insecticides, environmental management (EM) to control vector population (mainly Lutzomyia longipalpis phlebotomine), rigorous epidemiological surveillance, and health education. The present study was conducted in areas with recent moderate VL transmission to evaluate the efficacy of vector control activities. The systematic capture of phlebotomine was performed for three consecutive days per month, from August 2015 to July 2017. The number of specimens captured was taken as a representative of the monthly insect population. A total of 38,055 phlebotomine specimens were captured and identified at the species level. Lu. longipalpis was consistently found to be the predominant species (97.7%) each month. In the first year of the study, no intervention was performed. In the second year, two cycles of chemical spraying, EM, or a combination of both were performed before and after the rainy season. All interventions, either individually or in combination, reduced the abundance of Lu. longipalpis in the study area.

Treatment of Cutaneous Leishmaniasis in a Nonendemic Country: A Case Series of Children in Australia.

Hill, N., Irwin, A., Graham, N., Leung, C., Francis, J., Wall, N., Nourse, C.
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Pediatr Infect Dis J
https://doi.org/10.1097/INF.0000000000003445

We describe 4 cases of cutaneous leishmaniasis in children in Australia. Treatment is challenging given lack of firm guidelines and limited access to conventional modalities used in endemic countries. Topical paromomycin or oral fluconazole were effective outpatient-based first-line treatments, however, topical paromomycin use was limited by expense to import or compound locally.

Spatial modeling of zoonotic cutaneous leishmaniasis with regard to potential environmental factors using ANFIS and PCA-ANFIS methods.

Babaie, E., Alesheikh, A., Tabasi, M.
25-12-2021
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/34958766

This study compares two adaptive neuro-fuzzy inference system (ANFIS) and principal component analysis (PCA)-ANFIS techniques for spatial modeling and forecasting of zoonotic cutaneous leishmaniasis (ZCL) cases in rural districts of Golestan province, Iran. We collected and prepared data on ZCL cases and climatic, topographic, vegetation, and human population factors. By applying the PCA algorithm, the parameters affecting the ZCL incidence were decomposed into principal components (PCs), and their dimensions were reduced. Then, PCs were used to train the ANFIS model. To evaluate the proposed approaches in model assessment phase, we used test data in 2016. In this phase, we showed that PCA-ANFIS model with values of $R^2 = 0.791$, MAE = 0.681, RMSE = 0.904 compared to ANFIS model with values of $R^2 = 0.705$, MAE = 0.827, RMSE = 1.073 has better performance in prediction of the ZCL cases. Actual and

predicted maps of ZCL cases in 2016 by both models demonstrated that the high-risk regions of the disease are located in the northeastern, northern parts, and some central rural districts of Golestan province. Sensitivity analysis of the ANFIS model showed that population, vegetation, average wind speed, elevation, and average soil temperature, respectively, are the most significant factors in predicting the ZCL cases. The findings indicated the importance of machine learning (ML) techniques (ANFIS and PCA-ANFIS) in medical geography studies. By using these approaches, with less cost and shorter time, high-risk areas of diseases can be predicted, and the most effective factors on the spatial prediction of diseases can be identified. Public health policymakers can use these useful tools to control and prevent the disease and to allocate resources to disease-prone areas.

Update of the Phlebotominae Fauna with New Records for Argentina and Observations on Leishmaniasis Transmission Scenarios at a Regional Scale.

Moya, S., Szelag, E., Manteca-Acosta, M., Quintana, M., Salomón, O.
22-12-2021
Neotrop Entomol
https://doi.org/10.1007/s13744-021-00934-7

Phlebotominae are small insects distributed in the Americas from Canada to Argentina and Uruguay, counting with more than 500 neotropical species. Some of them have a vectorial role in the transmission of Leishmania Ross, the causative agent of leishmaniases, a group of worldwide distributed diseases with different clinical manifestations and transmission cycles. Our aim was to update the Phlebotominae fauna of Argentina and to make observations on the American Cutaneous (ACL) and Visceral Leishmaniasis (AVL) transmission scenarios, according to the distribution of proven or suspected Leishmania vector species and recent changes in land use. Primary data (entomological captures) and secondary data (review of 65 scientific publications with Phlebotominae records) were used. With 9 new records, 46 Phlebotominae species are now recorded through the area comprising 14 political jurisdictions and 6 phytogeographic provinces. Distribution maps were constructed for the 5 proven or incriminated Leishmania vector species, and the evidence supporting the vectorial incrimination of these species is discussed. Three main ACL transmission scenarios are described in the phytogeographic provinces of the Yungas, Chaco, and Paranaense, associated with deforestation processes, while the transmission scenarios of AVL are urban outbreaks and scattered cases in rural areas. We update the available knowledge on the Phlebotominae fauna present in Argentina, emphasizing its epidemiological relevance in the current context of the increasing frequency of ACL outbreaks and geographic spread of AVL.

[Erratum to: Visceral leishmaniasis mimicking Felty's syndrome in rheumatoid arthritis treated with methotrexate and etanercept].

Ruffer, N., Tomas, N., Schmiedel, S., Jordan, S., Kötter, I.
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Z Rheumatol
https://doi.org/10.1007/s00393-021-01143-8

Surveillance and genotype characterization of zoonotic trypanosomatidae in *Didelphis marsupialis* in two endemic sites of rural Panama.

Pineda, V., González, K., Perea, M., Rigg, C., Calzada, J., Chaves, L., Vásquez, V., Samudio, F., Gottdenker, N., Saldaña, A.
06-12-2021
Int J Parasitol Parasites Wildl
https://doi.org/10.1016/j.ijppaw.2021.12.002

Didelphis marsupialis has been reported as a competent reservoir for trypanosomatid parasites infections. The aim of this study was to measure *Trypanosoma cruzi, T. rangeli,* and *Leishmania* spp. infection rates and to characterize discrete typing units (DTUs) of *T. cruzi* in *D. marsupialis* from two Chagas disease endemic sites in Panama. Blood from 57 wild-caught *D. marsupialis* were examined from two rural communities, Las Pavas (N = 18) and Trinidad de las Minas (N = 39). Twenty-two (38.60%) opossums were positive for flagellates by general hemoculture. *T. cruzi* infection was confirmed by positive hemoculture and/or kDNA based PCR performed in 31/57 (54.39%) blood samples from opossums. *T. rangeli* infection was confirmed by hemoculture and/or TrF/R2-Primer PCR assay applied on 12/57 (21.05%) blood samples. Nine (15.79%) *D. marsupialis* harbored *T. cruzi/T. rangeli* coinfections. All opossums tested negative for *Leishmania* spp. by PCR assays based on kDNA and HSP70 gene amplification. There was a significant association between *T. cruzi* infection and site (Fisher exact test, p = 0.02), with a higher proportion of *T. cruzi* infected opossums in Las Pavas (77.78%, n = 14/18) compared to Trinidad de las Minas (43.59%, n = 17/39). A significant association was found between habitat type and *T. cruzi* infection in opossums across both communities, (X^2 = 6.91, p = 0.01, df = 1), with a higher proportion of *T. cruzi* infection in opossums captured in forest remnants (76%, 19/25) compared to peridomestic areas (37.5%, 12/32). *T. rangeli* detection, but not *T. cruzi* detection, may be improved by culture followed by PCR. TcI was the only DTU detected in 22 *T. cruzi* samples using conventional and real-time PCR. Eight *T. rangeli* positive samples were characterized as KP1(-)/lineage C. Trypanosome infection data from this common synanthropic mammal provides important information for improved surveillance and management of Chagas disease in endemic regions of Panama.

Live attenuated vaccines, a favorable strategy to provide long-term immunity against protozoan diseases.

Revue de littérature

Solana, J., Moreno, J., Iborra, S., Soto, M., Requena, J.
09-12-2021
Trends Parasitol
https://pubmed.ncbi.nlm.nih.gov/34896016

The control of diseases caused by protozoan parasites is one of the United Nations' Sustainable Development Goals. In recent years much research effort has gone into developing a new generation of live attenuated vaccines (LAVs) against malaria, Chagas disease and leishmaniasis. However, there is a bottleneck related to their biosafety, production, and distribution that slows downs further development. The success of irradiated or genetically attenuated sporozoites against malaria, added to the first LAV against leishmaniasis to be evaluated in clinical trials, is indicative that the drawbacks of LAVs are gradually being overcome. However, whether persistence of LAVs is a prerequisite for sustained long-term immunity remains to be clarified, and the procedures necessary for clinical evaluation of vaccine candidates need to be standardized.

Leishmania donovani and HIV co-infection in vitro: Identification and characterization of main molecular players.

Maksoud, S., Ortega, J., Hidalgo, M., Rangel, H.
23-11-2021
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/34822851

The incidence of Leishmania/HIV co-infection is growing and few studies detail the cellular processes and macromolecules participating in co-infection. Thus, the goal of this study was to partially describe the Leishmania/HIV co-infection events by measuring molecular and functional parameters associated with both pathogens in vitro. MT-4 cells (human T-lymphocytes), primary monocytes, and peripheral blood mononuclear cells were exposed to HIV and/or Leishmania donovani. The cytopathic effects generated by the pathogens were observed through microscopy. Viral replication was assessed by monitoring p24 protein levels and parasitic proliferation/infectivity was determined using Giemsa staining. Changes in molecular markers were evaluated by ELISA and fluorescence assays. Our results showed that our system reassembles the main parameters previously described for Leishmania/HIV co-infection in patients in terms of potentiation of parasitic and viral replication/infectivity, amplification of syncytia induction, and alterations of cell viability. In addition, an amplification in NF-κB activation, changes in CXCR4/CCR5 surface expression, and a Th1→Th2 variation in cytokine/chemokine secretion were demonstrated. Altogether, this study could contribute to gain a deep understanding of the molecular events associated with Leishmania/HIV co-infection.

[Visceral leishmaniasis mimicking Felty's syndrome in rheumatoid arthritis treated with methotrexate and etanercept].

Ruffer, N., Tomas, N., Schmiedel, S., Jordan, S., Kötter, I.
11-10-2021
Z Rheumatol
https://doi.org/10.1007/s00393-021-01105-0

Visceral leishmaniasis (VL) is a chronic parasitic disease caused by pathogens of the genus Leishmania, which can mimic numerous diseases. The leading symptoms of VL (splenomegaly, pancytopenia, fever) can be misinterpreted, especially if autoantibodies are detected, and lead to the misdiagnosis of an underlying rheumatic disease (e.g. systemic lupus erythematosus, Felty's syndrome). Proinflammatory cytokines such as tumour necrosis factor alpha (TNF-α) play an important role in infection control. In this context, there are increasing reports of VL as an opportunistic infection during treatment with anti-TNF-α agents. A case of VL mimicking Felty's syndrome in a patient with rheumatoid arthritis treated with methotrexate and etanercept is presented.

Exclusive Expression of MyD88 on Dendritic Cells Is Sufficient to Induce Protection against Experimental Leishmaniasis.

Lopez Kostka, S., Kautz-Neu, K., Yogev, N., Lukas, D., Holzmann, B., Waisman, A., Clausen, B., von Stebut, E.
24-09-2021
J Invest Dermatol
https://pubmed.ncbi.nlm.nih.gov/34570998

The overlooked value of training in self-administration of medication in Leishmania care: observations from the San Raffaele hospital ship humanitarian medical mission.

Manzano-Nunez, R., Restrepo-Holguin, D., Posso, D., López, A., Gómez, O.
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Trans R Soc Trop Med Hyg
https://doi.org/10.1093/trstmh/trab130

Thiohydantoins as anti-leishmanial agents: *n vitro* biological evaluation and multi-target investigation by molecular docking studies.

Camargo, P., Bortoleti, B., Fabris, M., Gonçalves, M., Tomiotto-Pellissier, F., Costa, I., Conchon-Costa, I., Lima, C., Pavanelli, W., Bispo, M., Macedo, F.
13-11-2020
J Biomol Struct Dyn
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Leishmaniasis is a neglected tropical disease caused by protozoa of the genus *Leishmania*. The first-line treatment of this disease is still based on pentavalent antimonial drugs that have a high toxicity profile, which could induce parasitic resistance. Therefore, there is a critical need to discover more effective and selective novel anti-leishmanial agents. In this context, thiohydantoins are a versatile class of substances due

to their simple synthesis and several biological activities. In this work, thiohydantoins **1a**-**l** were evaluated *in vitro* for antileishmania activity. Among them, four derivatives (**1c**, **1e**, **1h** and **1l**) showed promising IC_{50} values around 10 µM against promastigotes forms of *Leishmania amazonensis* and low cytotoxicity profile for peritoneal macrophages cells. Besides, these compounds induce oxidative stress through an increase in ROS production and the labeling of annexin-V and propidium iodide, indicating that promastigotes were undergoing a late apoptosis-like process. Additionally, molecular consensual docking analysis was carried out against two important targets to *L. amazonensis*: arginase and trypanothione reductase enzymes. Docking results suggest that thiohydantoin ring could be a pharmacophoric group due to its binding affinity by hydrogens bond interactions with important amino acid residues at the active site of both enzymes. These results demonstrate that compounds **1c**, **1e**, **1h** and **1l** may are promising in future advance studies.Communicated by Ramaswamy H. Sarma.

CYSTICERCOSE

Identification and characterization of sirtuin enzymes in cestodes and evaluation of sirtuin inhibitors as new cestocidal molecules.

Vaca, H., Celentano, A., Toscanini, M., Hauser, A., Macchiaroli, N., Cuestas, M., Nusblat, A., Sippl, W., Elissondo, M., Jung, M., Camicia, F., Rosenzvit, M.
09-02-2022
Int J Parasitol
https://pubmed.ncbi.nlm.nih.gov/35150663

Anti-parasitic treatment of neglected tropical diseases caused by cestodes such as echinococcosis and cysticercosis relies on a small number of approved anthelmintic drugs. Furthermore, the treatment is usually prolonged and often partially effective and not well tolerated by some patients. Therefore, the identification of novel drug targets and their associated compounds is critical. In this study, we identified and characterised sirtuin enzymes in cestodes and evaluated the cestocidal potential of sirtuin inhibitors as new cestocidal molecules. Sirtuins are a highly conserved family of nicotinamide-adenine dinucleotide-lysine deacylases involved in multiple cellular functions. Here, we described the full repertoire of sirtuin-encoding genes in several cestode species. We identified six sirtuin-encoding genes that were classified into sirtuins Class I (SIRT1, SIRT2, and SIRT3), Class III (SIRT5), and Class IV (SIRT6 and SIRT7). In Echinococcus spp., sirtuin genes showed transcriptional expression throughout several developmental stages, sirtuin 2 (SIRT2) being the most expressed. To evaluate the potential of sirtuin inhibitors as new cestocidal molecules, we determined the in vitro effect of several Class I sirtuin inhibitors by motility assay. Of those, the selective SIRT2 inhibitor Mz25 showed a strong cestocidal activity in Mesocestoides vogae (syn. Mesocestoides corti) tetrathyridia at various concentrations. The Mz25 cestocidal activity was time- and dose-dependent with a half-maximal inhibitory concentration value significantly lower than that of albendazole. Additionally, Mz25 induced extensive damage in the general morphology with marked alterations in the tegument and ultrastructural features. By homology modelling, we found that cestode SIRT2s showed a high conservation of the canonical sirtuin structure as well as in the residues related to Mz25 binding. Interestingly, some non-conservative mutations were found on the selectivity pocket (an Mz25-induced structural rearrangement on the active site), which represent a promising lead for developing selective cestode SIRT2 inhibitors derived from Mz25. Nevertheless, the Mz25 molecular target in M. vogae is unknown and remains to be determined. This report provides the basis for further studies of sirtuins to understand their roles in cestode biology and to develop selective sirtuin inhibitors to treat these neglected tropical diseases.

Subcutaneous cysticercosis due to Taenia crassiceps (Cestoda: Taeniidae) in an imported steppe lemming in Japan.

Chou, S., Ozawa, M., Matsubara, K., Tamukai, K., Tokiwa, T.
01-12-2021
Parasitol Int
https://pubmed.ncbi.nlm.nih.gov/34863980

This study describes a subcutaneous proliferative cysticercosis in a pet steppe lemming, Lagurus lagurus (Rodentia: Cricetidae), bred and imported from Czech Republic into Japan. Numerous metacestodes were collected from the subcutaneous cystic lesion of the left medial thigh. Four surgical removals were coupled with anthelmintic treatment but ended with recurrence. Based on morphological features and mitochondrial DNA sequences, the metacestodes were identified as the larval stage of Taenia crassiceps (Zeder, 1800). This is the first case of infection with larval T. crassiceps in rodents of the genus Lagurus, and becomes the third case of the parasite detected from imported animals in Japan. Related public health concerns are discussed.

Carbamazepine or levetiracetam: Which one is better in neurocysticercosis?

Panda, P., Sharawat, I.
31-03-2021
Acta Neurol Scand
https://doi.org/10.1111/ane.13424

DRACUNCULOSE

Description of new genus Baikalozercon (Acari: Mesostigmata: Zerconidae) with two new species from South Siberia Mountains (Russia).

Marchenko, I.
28-03-2022
Zootaxa
https://doi.org/10.11646/zootaxa.5120.3.1

This paper describes a new genus and two new species of mites in the family Zerconidae collected from litter and soil in the South Siberia Mountains. Baikalozercon gen. nov. is described to accommodate two new species B. dracunculus sp. nov. and B. irbis sp. nov. on the basis of adults specimens and immature stages. The new genus is characterised by unique characters such as very large size of idiosoma (9001000 m length); long peritremes in adults reaching to coxae I; sexual dimorphism of male gnathosomal structures; modified fixed digit of chelicerae with extended apical edge and large apical outgrowth; a pair of massive subcapitular denticles located between h3 and pc setae in B. dracunculus sp. nov.; and modified setae on legs II.

ECHINOCOCCOSE

23-year old man with a long history of abdominal pain, nausea and vomiting: Case report of a splenic cyst.

Senn, A., Bauer, R., Heigl, A., Rosenberg, R.
29-03-2022
Int J Surg Case Rep
https://pubmed.ncbi.nlm.nih.gov/35367949

Splenic cysts are rare. They are usually incidentally diagnosed and there is no harmonised treatment pathway. We report a case of a large splenic epidermoid type cyst without history of previous abdominal trauma. A 23-year old male patient presented with symptoms of upper abdominal pain, nausea and vomiting. Except for a tenderness in the upper and lower left quadrant of the abdomen, the initial examination showed no extraordinary findings. A contrast enhanced computed tomography revealed a large singular splenic cyst displacing neighbouring structures. Echinococcus serology was tested negative. A laparoscopic fenestration of the superficially located splenic cyst was performed. Perioperative course was free of complications. Histopathological analysis of the excisate showed a squamous lining indicating the cyst as epidermoid type. Non-parasitic cyst types include traumatic, neoplastic, degenerative and congenital cysts. Due to its considerable size, our patients splenic cyst was diagnosed after occurring symptoms lead to further examination (CT scan). Laparoscopic fenestration of the cyst was chosen as the optimal surgical approach because of the superficial location of the cyst and to preserve residual splenic parenchyma. In the present case, recurrence of the splenic cyst appeared, which left the patient with a total splenectomy as the final treatment choice. Due to the unspecific symptoms, the diagnosis of a splenic cyst can be prolonged. Choosing the adequate surgical technique to avoid complications is crucial. By deepening the understanding of the condition and surgical approaches, we can improve diagnostic and therapeutic management for affected patients.

Ruta graveolens, Peganum harmala, and Citrullus colocynthis methanolic extracts have in vitro protoscolocidal effects and act against bacteria isolated from echinococcal hydatid cyst fluid.

Al Qaisi, Y., Khleifat, K., Oran, S., Al Tarawneh, A., Qaralleh, H., Al-Qaisi, T., Farah, H.
30-03-2022
Arch Microbiol
https://doi.org/10.1007/s00203-022-02844-7

Echinococcosis is a common and endemic disease that affects both humans and animals. In this study, the in vitro activities of methanolic extracts of Ruta graveolens, Peganum harmala aerial parts, and Citrullus colocynthis seeds against protoscolosis and isolated bacterial strains from hydatid cysts were assessed using disc diffusion methods and Minimum Inhibitory Concentration (MIC). The chemical composition of three methanolic extracts was studied using LC-MS. After 3 h of exposure to 40 mg/mL R. graveolens extract, a tenfold protoscolocidal effect was seen when compared to the convintional medication (ABZ) for the same duration ($P<0.05$). The bacteria listed below were isolated from hydatid cyst fluid collected from a variety of sick locations, including the lung and liver. Micrococcus spp., E. coli, Klebsiella oxytoca, Enterobacter aerogenes, Enterobacter amnigenus, Pseudomonas aeruginosa, Staphylococcus xylosus, and Achromobacter xylosoxidans are among the bacteria that have been identified. The most effective extract was R. graveolens, followed by P. harmala and C. colocynthis, according to the results of antibacterial activity using the disc diffusion method. R. graveolens extract had the lowest MIC values (less than 2 mg/mL) against all microorganisms tested. This shows that the R. graveolens extract has additional properties, such as the ability to be both scolocidal and bactericidal. Because these bacteria are among the most prevalent pathogenic bacteria that increase the risk of secondary infection during hydatid cysts, the results of inhibitory zones and MICs of the R. graveolens methanol extract are considered highly promising.

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

Casulli, A., Massolo, A., Saarma, U., Umhang, G., Santolamazza, F., Santoro, A.
28-03-2022
Parasit Vectors

https://doi.org/10.1186/s13071-022-05197-8

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

Anthelmintic activity of *Stevia multiaristata* extract against *Echinococcus granulosus sensu stricto*.

Albani, C., Borgo, J., Fabbri, J., Pensel, P., Fasciani, L., Elso, O., Papademetrio, D., Grasso, D., Paladini, A., Beer, M., Farias, N., Elissondo, N., Gambino, G., Zoppi, J., Sülsen, V., Elissondo, M.

13-12-2021

Parasitology

https://doi.org/10.1017/S0031182021002109

Cystic echinococcosis is a zoonotic disease caused by the larval stage of the parasite Echinococcus granulosus sensu lato. The available anti-parasitic treatment is mostly limited to a continuous administration of albendazole. However, due to its numerous side-effects and efficacy of around 50%, there is a need to find new drugs to improve the treatment for this disease. In the current study, the in vitro and in vivo efficacy of a Stevia multiaristata extract against E. granulosus sensu stricto (s.s.) was demonstrated. Stevia multiaristata extract (100 and 50 µg mL−1) caused a quick viability decrease on protoscoleces which was consistent with the observed tegumental alterations. Loss of turgidity was detected in 95 ± 3.4% of cysts incubated with S. multiaristata extract during 2 days (100 µg mL−1) and the collapse of the germinal layer was observed in 60 ± 9.3% of cysts treated with 100 µg mL−1 of the S. multiaristata extract during 4 days. The half maximal effective concentration value was 69.6 µg mL−1 and the selectivity index for E. granulosus s.s. cysts was 1.9. In this clinical efficacy study, the treatment of infected mice with the S. multiaristata extract (50 mg kg−1) caused a significant decrease in the weight of the cysts compared with the control group. These results coincided with the tissue damage observed in the cysts at the ultrastructural level. In conclusion, we observed high protoscolicidal and cysticidal effects, and significant reduction in the weight of the cysts in experimentally infected mice following treatment with the S. multiaristata extract.

A Large Hydatid Cyst in the Brain of a 10-year Child.

Ashraf, M., Ahmed, S., Ahmad, S., Ahmad, A.

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J Coll Physicians Surg Pak

https://doi.org/10.29271/jcpsp.2022.04.538

Hydatid cyst is the larval form of the parasite, echinococcus granulosus. We operated upon a case of a giant hydatid cyst in the left cerebral hemisphere of a 10-year male child. The patient presented to us with a history of headache, vomiting, vertigo and difficulty in walking. On the examination, there was hemiparesis on the right side and left-sided papilledema. The CT scan showed a large extra-axial cystic lesion in the left frontotemporoparietal area. Craniotomy and excision of the cyst by hydro-dissection was performed. The patient recovered uneventfully and was discharged. Albendazole was given postoperatively for a period of one month. The follow-up CT scan, performed after three months, showed complete resolution of the disease. Key Words: Hydatid cyst, Echinococcus granulosus, Brain, Children.

Echinococcus multilocularis drives the polarization of macrophages by regulating the RhoA-MAPK signaling pathway and thus affects liver fibrosis.

Chong, S., Chen, G., Dang, Z., Niu, F., Zhang, L., Ma, H., Zhao, Y.

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Bioengineered

https://doi.org/10.1080/21655979.2022.2056690

Echinococcus multilocularis is a small parasite that causes alveolar echinococcosis. It primarily induces liver disorder, such as liver fibrosis and even liver cancer, which severely endangers human lives. This study aims to explore the efficacy of *Echinococcus multilocularis* soluble antigen in preventing and alleviating alveolar echinococcosis-induced liver fibrosis and determine the underlying mechanism. We first identified the optimal dose and time of *Echinococcus multilocularis* soluble antigen. The protein levels of key genes in the RhoA-MAPK signaling pathway were remarkably upregulated in

RAW264.7 and Ana-1 cells induced with 80 µg/mL *Echinococcus multilocularis* soluble antigen for 8 h. Interestingly, the upregulated expression levels were remarkably reversed by the RhoA, JNK, ERK, or p38 inhibitor, confirming the significance of the RhoA-MAPK signaling pathway. In addition, the relative contents of M2 polarization markers IL-10 and Arg-1 in macrophages induced with 80 µg/mL *Echinococcus multilocularis* soluble antigen for 8 h increased, whereas those of M1 polarization markers IL-12 and NOS-2 decreased. Mouse hepatic stellate cells were the key components of the hepatocellular carcinoma tumor microenvironment. Hepatic stellate cells were activated by *Echinococcus multilocularis* soluble antigen and transformed into the morphology of myofibroblasts in response to liver disorders. By detecting the marker of myofibroblast formation, RhoA inhibitor remarkably reduced the positive expression of α-SMA in mouse hepatic stellate cells induced with *Echinococcus multilocularis* soluble antigen. Therefore, *Echinococcus multilocularis* soluble antigen remarkably activated the RhoA-MAPK pathways in macrophages, further inducing the polarization of macrophages and ultimately causing liver fibrosis. We hypothesize that infection with *Echinococcus multilocularis* activates the RhoA-MAPK signaling pathway and subsequently induces macrophage polarization to promote hepatic stellate cells activation leading to liver fibrosis. To investigate the mechanism by which soluble antigen of *Echinococcus multilocularis* affects liver fibrosis through the RhoA-MAPK pathway driving polarization of macrophages. To identify new pathways of intervention and drug targets for the regulation of macrophage polarity phenotype switching and the attenuation or inhibition of the development and treatment of liver fibrosis caused by *Echinococcus multilocularis* infection.

Assessing the potential for infections of Echinococcus multilocularis in dogs in a hotspot of human alveolar echinococcosis infections in North America.

Porter, E., Seguin, M., Estrada, M., Szlosek, D., Massolo, A., Visscher, D.
09-02-2022
Vet Parasitol Reg Stud Reports
https://pubmed.ncbi.nlm.nih.gov/35256128

Echinococcus multilocularis is a zoonotic tapeworm, whose metacestode larval stage is the etiological agent for alveolar echinococcosis in humans and is a parasite of emerging concern according to the World Health Organization which is difficult to diagnose and has a case mortality rate of >90% when left untreated. Echinococcus multilocularis requires two mammalian hosts to complete its lifecycle: wild and domestic canids as definitive hosts, and small mammals (mostly rodents) as intermediate ones. Because of their close relations with humans, domestic dogs have been indicated as a mean of infection to people. Human alveolar echinococcosis has historically been rare in North America, however, since 2013, at least seventeen diagnoses have been confirmed in Alberta, Canada. Because of this unprecedented series of cases, assessing the frequency of infections in dogs in Alberta is key to estimate risk for dog owners and animal health professionals. This study was carried out in Edmonton to determine the frequency of E. multilocularis infection in domestic dogs and potential risk factors. Fecal samples and corresponding behavior risk surveys were collected from 775 dogs in seven urban off-leash parks within Edmonton city limits during the summer of 2020. A quantitative PCR fecal test was used to diagnose E. multilocularis infection. We found a single case of E. multilocularis infection (1/775) and determined that the overall true prevalence was 0.2% (95% CrI: 0.0-0.7%) corrected for detection sensitivity and specificity. Overall, these findings confirm the presence of E. multilocularis infection in domestic dogs in Edmonton although further work is required to fully understand the risk factors that may contribute to infection and potential transmission to humans.

Identification and characterization of sirtuin enzymes in cestodes and evaluation of sirtuin inhibitors as new cestocidal molecules.

Vaca, H., Celentano, A., Toscanini, M., Hauser, A., Macchiaroli, N., Cuestas, M., Nusblat, A., Sippl, W., Elissondo, M., Jung, M., Camicia, F., Rosenzvit, M.
09-02-2022
Int J Parasitol
https://pubmed.ncbi.nlm.nih.gov/35150663

Anti-parasitic treatment of neglected tropical diseases caused by cestodes such as echinococcosis and cysticercosis relies on a small number of approved anthelmintic drugs. Furthermore, the treatment is usually prolonged and often partially effective and not well tolerated by some patients. Therefore, the identification of novel drug targets and their associated compounds is critical. In this study, we identified and characterised sirtuin enzymes in cestodes and evaluated the cestocidal potential of sirtuin inhibitors as new cestocidal molecules. Sirtuins are a highly conserved family of nicotinamide-adenine dinucleotide-lysine deacylases involved in multiple cellular functions. Here, we described the full repertoire of sirtuin-encoding genes in several cestode species. We identified six sirtuin-encoding genes that were classified into sirtuins Class I (SIRT1, SIRT2, and SIRT3), Class III (SIRT5), and Class IV (SIRT6 and SIRT7). In Echinococcus spp., sirtuin genes showed transcriptional expression throughout several developmental stages, sirtuin 2 (SIRT2) being the most expressed. To evaluate the potential of sirtuin inhibitors as new cestocidal molecules, we determined the in vitro effect of several Class I sirtuin inhibitors by motility assay. Of those, the selective SIRT2 inhibitor Mz25 showed a strong cestocidal activity in Mesocestoides vogae (syn. Mesocestoides corti) tetrathyridia at various concentrations. The Mz25 cestocidal activity was time- and dose-dependent with a half-maximal inhibitory concentration value significantly lower than that of albendazole. Additionally, Mz25 induced extensive damage in the general morphology with marked alterations in the tegument and ultrastructural features. By homology modelling, we found that cestode SIRT2s showed a high

conservation of the canonical sirtuin structure as well as in the residues related to Mz25 binding. Interestingly, some non-conservative mutations were found on the selectivity pocket (an Mz25-induced structural rearrangement on the active site), which represent a promising lead for developing selective cestode SIRT2 inhibitors derived from Mz25. Nevertheless, the Mz25 molecular target in M. vogae is unknown and remains to be determined. This report provides the basis for further studies of sirtuins to understand their roles in cestode biology and to develop selective sirtuin inhibitors to treat these neglected tropical diseases.

In vitro efficacy of Capparis spinosa extraction against larvae viability of Echinococcus granulosus sensu stricto.

Yan, M., Li, J., Liu, H., Yang, N., Chu, J., Sun, L., Bi, X., Lin, R., Lv, G.
07-03-2022
J Vet Med Sci
https://doi.org/10.1292/jvms.21-0609

Cystic echinococcosis (CE) is a chronic zoonotic parasitic disease caused by infection with the larvae of the Echinococcus granulosus sensu lato (s.l.) cluster. Currently, new drugs are urgently required due to the poor therapeutic effect of the existing drugs albendazole and mebendazole. Capparis spinosa, a traditional medicinal plant, has potential therapeutic effects on various diseases based on extracts from its fruit and other parts. The results of this study demonstrated that the water-soluble and ethanolic extracts of C. spinosa fruit had in vitro killing effects on the larvae of E. granulosus sensu stricto (s.s.) and disrupted the ultrastructure of protoscoleces and metacestodes. In vitro cytotoxicity assays showed that the water-soluble and ethanolic extracts of C. spinosa fruit were not significantly toxic to primary mouse hepatocytes at an effective dose to CE. In conclusion, water-soluble and ethanolic extracts of C. spinosa fruit have great potential for the development of new drugs for the treatment of CE.

Autocrine osteopontin is involved in maintaining the growth and metastasis of Echinococcus multilocularis.

Yang, H., Zhang, H., Yang, J., Liu, S., Zhang, S.
24-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35085512

Alveolar echinococcosis is a zoonotic disease that seriously endangers human health. This study aims to investigate the effects of osteopontin on the growth and intra- or extra-hepatic metastasis of Echinococcus multilocularis. Mice were randomly divided into untreated (control group, n = 25), PBS (n = 25), Lv3-NC (n = 25), and Lv-OPN-734 (n = 25) groups. Knockdown OPN by injecting lentivirus through the intraperitoneal portal vein, the metastatic lesions infected with Echinococcus multilocularis and adjacent liver tissues were observed, and the expression of osteopontin and epidermal growth factor receptor pathway-related molecules were studied. Gross observation of specimens suggested that there was no extra- hepatic metastasis, and mild intrahepatic invasion was observed in the Lv-OPN-734 group after 4 months of infection, and lung metastasis occurred in the Lv3-NC group. Western-blot and immunohistochemical staining results showed that the protein expression of OPN, phosphorylation of epidermal growth factor receptor and downstream molecules of the pathway decreased significantly after osteopontin knockdown, whereas the levels of non-phosphorylated proteins did not change significantly. In human tissues, through western-blot and immunohistochemical staining we found that compared with the control group, the expression of OPN in the liver tissues infected with Echinococcus multilocularis were higher than that in the control group. These findings indicate that osteopontin is involved in maintaining the growth and metastasis of Echinococcus multilocularis, suggesting that osteopontin may be a potential target for the treatment of alveolar echinococcosis.

Transcriptional effects of electroporation on Echinococcus multilocularis primary cell culture.

Pérez, M., Rego, N., Spiliotis, M., Brehm, K., Rosenzvit, M.
26-01-2022
Parasitol Res
https://doi.org/10.1007/s00436-022-07427-5

Echinococcus multilocularis is the etiological agent of alveolar echinococcosis (AE), a serious parasitic disease in the Northern Hemisphere. The E. multilocularis primary cell cultivation system, together with E. multilocularis genome data and a range of pioneering molecular-based tools have advanced the research on this and other cestodes. RNA interference (RNAi) and microRNA knock-down have recently contributed to the study of the cellular and molecular basis of tapeworm development and host-parasite interaction. These, as well as other techniques, normally involve an electroporation step for the delivery of RNA, DNA, peptides, and small molecules into cells. Using transcriptome data and bioinformatic analyses, we herein report a genome-wide comparison between primary cells of E. multilocularis and primary cells under electroporated conditions after 48 h of culture. We observed that~15% of genes showed a significant variation in expression level, including highly upregulated genes in electroporated cells, putatively involved in detoxification and membrane remodeling. Furthermore, we found genes related to carbohydrate metabolism, proteolysis, calcium ion binding and microtubule processing significantly altered, which could explain the cellular dispersion and the reduced formation of cellular aggregates observed during the first 48 h after electroporation.

Sensitivity comparison between Mini-FLOTAC and conventional techniques for the detection of Echinococcus multilocularis eggs.

Kida, I., Kouguchi, H., Irie, T., Yagi, K., Nakao, R., Nonaka, N.
02-12-2021
Parasitol Int
https://pubmed.ncbi.nlm.nih.gov/34863981

Canines serve as the definitive host of Echinococcus multilocularis. This study evaluated the sensitivity of the Mini-FLOTAC technique (MF) for the detection of E. multilocularis eggs in definitive hosts. First, we investigated the effects of heat inactivation and preservative conditions on the detection rate of eggs obtained from experimentally infected dogs. The sensitivity of MF was compared with that of eight other techniques: the centrifugal flotation with sucrose or zinc sulfate, MGL, AMS III, and a combination of MF and flotation/sedimentation techniques. Finally, we compared the sensitivity of MF and the centrifugal flotation with sucrose for the feces of E. multilocularis-infected foxes. The detection rate reached a plateau level with a specific gravity (s.g.) 1.22 for fresh eggs, but the highest rates were obtained with s.g. greater than 1.32 for heat-inactivated eggs. There was no significant difference in the detection rate among the preservative conditions. MF showed significantly higher EPG than the other techniques. Moreover, it showed higher diagnostic sensitivity for the fox feces than the centrifugal flotation technique. These results suggest that heat inactivation may alter s.g. of E. multilocularis eggs and that MF with zinc sulfate (s.g. = 1.32) would be effective for detecting heat-inactivated E. multilocularis eggs.

Factors Affecting the Choice of Treatment in Hepatic Hydatid Cyst Surgery.

Cantay, H., Anuk, T.
21-06-2021
J Invest Surg
https://doi.org/10.1080/08941939.2021.1924900

We aimed to determine the effective factors in the selection of treatment methods for patients with hepatic hydatid cyst undergoing surgery and the variables effective when performing postoperative endoscopic retrograde cholangiopancreatography (ERCP). In addition, we aimed to reveal the factors affecting the recurrence, postoperative complications, and length of stay of these patients. A total of 107 patients diagnosed with hepatic hydatid cysts were treated surgically. Data were obtained from the records of these patients. Chi-square test was used for the analysis. The variables that were found to be significant in the chi-square analysis were included in the logistic regression (Backward: LR) analysis. Of all patients, 6.5% underwent the puncture, aspiration, injection, and reaspiration (PAIR) technique, 67.3% underwent conservative surgery, and 26.2% underwent radical surgical treatment. In paired comparisons, a significant difference was found among the ultrasonographic size of the cyst (p=0.033), the radiological classification of the cyst (0.006), and history of previous surgery and treatment methods for the cyst. The risk of performing ERCP was 25.710 [95% confidence interval (CI): 1.721-284.013] folds higher for cysts located in the left lobe, whereas it was 19.992 (95% CI: 2.004-199.488) folds higher for cysts located in both right and left lobes. When the radical surgical treatment method was taken as a reference, the status of ERCP implementation was 29.785 (95% CI: 1.844-480.996) folds higher for PAIR and 3.628 (95% CI: 0.355-37.103) folds higher for conservative surgery. In conclusion, radical surgery is a significant treatment for hepatic hydatid cyst as its ultrasonographic cyst size increases with time. The location and treatment method of the cyst increases the complication of biliary fistula and requires ERCP.

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

Body condition scores, fluke intensity, liver pathology, and carcass quality of different dairy cattle genotypes infected with Fasciola species at high throughput abattoirs in South Africa.

Mpisana, Z., Jaja, I., Byaruhanga, C., Marufu, M.
02-04-2022
Parasitol Res
https://doi.org/10.1007/s00436-022-07504-9

Milk is an essential commodity whose demand far exceeds supply. However, dairy animal productivity is constantly hampered by parasitic diseases such as fasciolosis, affecting milk production. Despite the negative impact of liver fluke on milk production, there is little information on liver fluke infection and associated abattoir losses (body weight, condition score, liver pathology, and carcass quality) in culled dairy cattle. This study aimed to determine body condition scores, fluke intensity, liver pathology, and carcass quality of different cattle genotypes infected with Fasciola species at three commercial abattoirs. A longitudinal study was conducted from September 2019 to October 2020 to determine body condition score, liver fluke intensity, liver pathology in 3065 dairy cattle slaughtered in CA1, CA2, and CA3, of the Eastern Cape Province South Africa. Liver fluke intensity significantly increased with cattle age (P<0.0001). Cattle≥7 years old (59.93±6.42) and those 4 to 6 years old (49.78±9.98) had higher infection than those 2 to 3 years old (27.55±13.68). The liver fluke infection was significantly (P<0.001) the highest when sampling was conducted in summer, followed by autumn and winter, and least for spring. The differences in carcass weights or body condition scores decreased by 0.99 units (P<0.0001) or 0.97 units (P<0.0001) respectively. Therefore, this study suggests that fluke infection could be responsible for considerable economic and production losses mainly due to condemnation and weight loss in dairy cattle. This study recommended a combination of holistic and grazing management to control infection rates in

dairy herds.

The causative agents of fascioliasis in animals and humans: Parthenogenetic Fasciola in Asia and other regions.

Itagaki, T., Hayashi, K., Ohari, Y.
17-02-2022
Infect Genet Evol
https://pubmed.ncbi.nlm.nih.gov/35183754

Parthenogenetic Fasciola is the causative agent of fascioliasis in animals and humans and is widely distributed in Asian countries, such as Japan, South Korea, China, Vietnam, Thailand, the Philippines, Myanmar, Bangladesh, Nepal, and India. Parthenogenetic Fasciola geographically originated from central and eastern China, where it exists between the habitats of Fasciola hepatica and Fasciola gigantica; it likely appeared thousands of years ago following hybridization between F. hepatica and F. gigantica. Parthenogenetic Fasciola consists of diploids and triploids that possess nuclear genome of both F. hepatica and F. gigantica and mitochondrial genome of either F. hepatica or F. gigantica. Maternal parents of parthenogenetic Fasciola are either F. hepatica having Fh-C4 haplotype or F. gigantica having Fg-C2 haplotype in mitochondrial NADH dehydrogenase subunit 1 (ND1) nucleotide sequences. Parthenogenetic Fasciola flukes with the Fh-C4 haplotype have spread from China to South Korea and Japan, whereas the flukes with the Fg-C2 haplotype have not only spread to Korea and Japan but also southward to Vietnam, Thailand, the Philippines, Myanmar, Bangladesh, Nepal, and India. Parthenogenetic Fasciola can be distinguished from F. hepatica and F. gigantica using combinational DNA sequence analysis of nuclear phosphoenolpyruvate carboxykinase (pepck) and DNA polymerase delta (pold) along with mitochondrial ND1 markers. The establishment of parthenogenetic Fasciola is expected as follows: parthenogenetic diploids with the Fh-C4 and Fg-C2 haplotypes first appeared based on single or multiple interspecific hybridization events; subsequently, parthenogenetic triploids emerged via backcross events between the maternal parthenogenetic diploid and either paternal bisexual F. hepatica or F. gigantica. Parthenogenetic Fasciola diploids and triploids then survived for thousands of years by clonal parthenogenetic reproduction, and generated descendants with ND1 haplotypes, which were derived from the Fh-C4 and Fg-C2 due to nucleotide substitution. Thus, the emergence of parthenogenetic Fasciola may be due to extremely uncommon and accidental events. Parthenogenetic Fasciola should be treated as a new asexual hybrid species.

Helminth antigens modulate human PBMCs, attenuating disease progression in a humanised mouse model of graft versus host disease.

Healy, M., Aldridge, A., Glasgow, A., Mahon, B., English, K., O'Neill, S.
11-02-2022
Exp Parasitol
https://pubmed.ncbi.nlm.nih.gov/35151653

Fasciola hepatica is a trematode worm that causes fascioliasis, a neglected tropical disease in humans and livestock. To gain insight into the host-parasite interactions that facilitate infection, we have investigated the immunomodulatory properties of the parasite's tegumental coat (FhTeg), a major antigen source that is sloughed off and renewed every 2-3 h as the worm migrates through host tissue. Using mouse models of infection, we have previously shown that FhTeg induces a novel phenotype of dendritic cells that induce anergic $CD4^+$ T-cells. We proposed that this induced state of hyporesponsiveness characterised by suppression of cell proliferation and cytokine secretion was one mechanism by which F. hepatica prevented host protective immunity to support the parasite survival. To determine if the same mechanisms are utilised during human infections, we have now examined the interaction of FhTeg with human PBMCs. FhTeg binds to and modulates cytokine production in human PBMCs, in particular targeting the $CD4^+$ population resulting in reduced levels of TNF, IL-2 and IFNγ and increased markers of anergy. Furthermore, the adoptive transfer of FhTeg stimulated PBMCs to a humanised model of acute graft versus host disease (GvHD) attenuated disease progression by increasing survival and reducing pathological scores. These mice also displayed a significant decrease in the total number of human $CD4^+$ cells expressing TNF, IL-2 and IFNγ in the spleen, liver and lung. This study therefore concurs with evidence from ruminant and murine models of infection suggesting that anergic $CD4^+$ T cells are associated with successful Fasciola hepatica infection and highlights an important role for FhTeg in contributing to the overall immunosuppressive effects of this parasite.

Sporadic endemicity of zoonotic Paragonimus in raccoon dogs and Japanese badgers from Miyazaki Prefecture, Japan.

Ishida, M., Kaneko, C., Irie, T., Maruyama, Y., Tokuda, A., Yoshida, A.
03-03-2022
J Vet Med Sci
https://doi.org/10.1292/jvms.21-0573

Paragonimiasis is a zoonotic trematode infection caused by Paragonimus spp. To determine the recent status of Paragonimus infections in wild animals, this study investigated Paragonimus spp. in 39 raccoon dogs and 54 Japanese badgers from March 2019 to January 2021 in Miyazaki Prefecture, and examined metacercariae in freshwater crabs. Triploid P. westermani was found in one raccoon dog (2.6%), and metacercariae were recovered from Eriocheir japonica captured near the infected animal collected. One Japanese badger (1.9%) harbored P. skrjabini miyazakii; this prevalence was lower than the approximately 30% that was reported in the 1970s. Results indicated that zoonotic Paragonimus was sporadically prevalent in wild animals. Further investigation in various animals is awaited to elucidate current wildlife reservoirs for those Paragonimus.

Spatial visualization of drug uptake and distribution in Fasciola hepatica using high-resolution AP-SMALDI mass spectrometry imaging.

Morawietz, C., Peter Ventura, A., Grevelding, C., Haeberlein, S., Spengler, B.
24-01-2022
Parasitol Res
https://doi.org/10.1007/s00436-021-07388-1

Understanding drug penetration, distribution, and metabolization is fundamental for understanding drug efficacy. This also accounts for parasites during antiparasitic treatment. Recently, we established matrix-assisted laser desorption/ionization (MALDI) mass spectrometry imaging (MSI) in blood flukes and liver flukes. This label-free technique is capable of visualizing the molecular distribution of endogenous and exogenous molecules, such as drug compounds. Here, we conducted atmospheric-pressure scanning microprobe MALDI MSI (AP-SMALDI MSI) of tissue sections of adult Fasciola hepatica that have been treated in vitro with 100 µM of triclabendazole (TCBZ), the drug of choice for treatment of fasciolosis, and its main metabolite triclabendazole sulfoxide (TCBZ-SO). Measurements covered an m/z mass range of 250-1,000 and provided a high spatial resolution using a pixel size of 10 µm. To support the interpretation of drug distribution, we first identified endogenous lipids that mark characteristic tissues such as the gastrodermis, the tegument, and the parenchyma. The obtained results suggested an early tegumental route of TCBZ uptake within 20 min, followed by spreading throughout the parasite after 4 h, and an even distribution in most tissues after 12 h. This coincided with a strong reduction of parasite vitality. TCBZ-SO treatment demonstrated the accumulation of this metabolite in the same tissues as the parent drug compound. These data demonstrate the auspicious potential of MALDI MSI to visualize uptake and distribution patterns of drugs or drug-candidate compounds in parasites, which might contribute to preclinical drug discovery in liver fluke research and beyond.

Time-dependent renal pathologies associated with the liver fluke infection, opisthorchiasis felinea.

Kapushchak, Y., Zaparina, O., Mordvinov, V., Pakharukova, M.
23-12-2021
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/34954256

Fish-borne trematode infections affect the health of more than 18 million people in Russia and Asian countries. Infection of humans and other mammals with the liver fluke Opisthorchis felineus (Rivolta, 1884) is accompanied by gradual development of liver disorders. Although there is indirect evidence that opisthorchiasis may be associated with damage to other organs, direct evidence of the connection between opisthorchiasis felinea and a kidney pathology has not yet been reported. To gain first insights into the possible relation, we investigated time course profiles of blood markers of renal failure as well as renal histological changes during opisthorchiasis from 1 month to 1.5 years postinfection in golden hamsters Mesocricetus auratus. For the first time, we showed that opisthorchiasis felinea leads to the development of glomerulopathy. In particular, O. felineus infection provoked gradual increases in serum creatinine, serum glucose, and urine protein concentrations. Moreover, there was gradual accumulation of renal tubular casts and of the mesangial matrix. Although the mechanisms underlying these renal pathologies remain unclear and require further research, we can conclude that O. felineus infection causes gradual progression of glomerulopathy accompanied by tubulopathy. Thus, overall, these aberrations correlate with the time course of hepatic pathological changes in opisthorchiasis felinea.

FILARIOSE LYMPHATIQUE

Rare Cases of Filarial Chyluria in Children.

Srivastava, S., Tiwari, V., Sen, M.
30-03-2022
Int Med Case Rep J
https://doi.org/10.2147/IMCRJ.S339207

Lymphatic filariasis leading to the passage of white urine or chyle is a rare manifestation in children. Filarial parasite infiltration leading to abnormal lymphatic-urinary communication occurs with prolonged infection. The incubation period ranges from 5 to 20 yrs., thus relatively infrequent in the pediatric age group. Index of suspicion should be high when a child presents with the passage of white urine because the subclinical manifestation of filarial infection is difficult to recognize. Moreover, more pathognomonic clinical manifestations such as lymphoedema or hydrocoele are present in adulthood. It should also be differentiated from non-parasitic causes like nephrotic syndrome, urates and phosphates in urine, and congenital lymphatic-urinary communication. We report two pediatric cases with the intermittent passage of milky white urine since one year. Institutional ethical committee approved the study. In both patients, urine triglycerides were high, and the presence of positive filarial antigen test confirmed the diagnosis. Medical management showed remission of symptoms. Our cases highlight the rare presentation of LF in children and the use of point of care diagnostic tests, management, and outcome in them. LF is a rare condition in children, and the index of suspicion should be high for early management.

Wolbachia depletion blocks transmission of lymphatic filariasis by preventing chitinase-dependent parasite exsheathment.

Quek, S., Cook, D., Wu, Y., Marriott, A., Steven, A., Johnston, K., Ford, L., Archer, J., Hemingway, J., Ward, S., Wagstaff, S., Turner, J., Taylor, M.
04-04-2022

Proc Natl Acad Sci U S A
https://doi.org/10.1073/pnas.2120003119

Significance Lymphatic filariasis caused by *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori* affects 51 million people, leading to severe physical and mental disabilities. A mutualistic symbiosis between these filarial nematodes and *Wolbachia* bacteria has been exploited as a new curative treatment. Epidemiological modeling of anti-*Wolbachia* treatment assumes that transmission persists due to the lag phase before microfilariae (mf) become removed from circulation. Here, we show that *Wolbachia*-depleted mf cannot develop within the mosquito vector-a phenotype associated with down-regulation of *B. malayi* mf-specific chitinase, an enzyme essential for exsheathment. Our findings add to the broad range of host biological processes dependent on *Wolbachia* and suggest that anti-*Wolbachia* treatment mediates a more accelerated impact on elimination of lymphatic filariasis than currently predicted.

Neutrophils: Friend or Foe in Filariasis?

Revue de littérature

Ajendra, J., Allen, J.
04-04-2022
Parasite Immunol
https://doi.org/10.1111/pim.12918

Infection with the filarial nematodes that cause diseases such as lymphatic filariasis and onchocerciasis represent major public health challenges. With millions of people at risk of infection, new strategies for treatment or prevention are urgently needed. More complete understanding of the host immune system's ability to control and eliminate the infection is an important step towards fighting these debilitating infectious diseases. Neutrophils are innate immune cells that are rapidly recruited to inflamed or infected tissues and while considered primarily anti-microbial, there is increasing recognition of their role in helminth infections. Filarial nematodes present a unique situation, as many species harbour the bacterial endosymbiont, Wolbachia. The unexpected involvement of neutrophils during filarial infections has been revealed both in human diseases and animal studies, with strong evidence for recruitment by Wolbachia. This present review will introduce the different human filarial diseases and discuss neutrophil involvement in both protective immune responses, but also in the exacerbation of pathology. Additionally, we will highlight the contributions of the murine model of filariasis, Litomosoides sigmodontis. While several studies have revealed the importance of neutrophils in these parasite infections, we will also draw attention to many questions that remain to be answered.

Family-based intervention for prevention and self-management of disabilities due to leprosy, podoconiosis and lymphatic filariasis versus usual care in Ethiopia: study protocol for a cluster-randomised controlled trial.

van 't Noordende, A., Aycheh, M., Moges, N., Tadesse, T., Schippers, A.
30-03-2022
BMJ Open
https://doi.org/10.1136/bmjopen-2021-056620

Leprosy, podoconiosis and lymphatic filariasis (LF) are three skin-related neglected tropical diseases. All three conditions can lead to temporary and permanent impairments. These impairments progressively worsen and are major determinants of stigma, discrimination and participation restrictions. Self-care is essential to prevent disabilities and chronic disease complications. Many persons with leprosy-related, LF-related and podoconiosis-related disabilities need to practice self-management routines their entire life. This is difficult without support and encouragement of others. The objective of this study was to assess the effectiveness of a family-based intervention in terms of physical outcomes related to prevention and self-management of disabilities due to leprosy, podoconiosis and LF and family quality of life and well-being compared with usual practice and care. The study will use a cluster-randomised controlled trial design with two study arms. The project will be carried out in endemic districts in East and West Gojjam zones in the Amhara region in Ethiopia. Clusters consist of kebeles (lower administrative structures in the district) that have been merged, based on their geographical proximity and the number of cases in each kebele. A total of 630 participants will be included in the study. The intervention group will consist of 105 persons affected by leprosy, 105 persons affected by LF or podoconiosis, and 210 family members. The control group will consist of 105 persons affected by leprosy and 105 persons affected by LF or podoconiosis. The family-based intervention comprises an essential care package that consists of the following three main components: (1) self-management of disabilities, (2) economic empowerment and (3) psychosocial support. Participants in the control areas will receive usual practice and care. Data analysis includes, but is not limited to, calculating the percentage of change and corresponding 95%CI of physical impairment outcomes in each group, before and after the intervention is implemented, effect sizes, intention to treat and difference in difference analysis. Ethical approval has been obtained from the Debre Markos University Health Sciences Institutional Research Ethics Review Committee. Results will be disseminated through peer-reviewed publications, conference presentations and workshops. PACTR202108907851342.

Efficacy and safety of triple therapy versus dual therapy for lymphatic filariasis: Discordance between conclusion and findings.

Cheema, H., Shahid, A.
02-03-2022

Trop Med Int Health
https://doi.org/10.1111/tmi.13740

Authors' Response to "Efficacy and safety of triple therapy versus dual therapy for lymphatic filariasis: Discordance between the conclusion and the findings".

Abuelazm, M., Abdelazeem, B., Abd-Elsalam, S.
03-03-2022
Trop Med Int Health
https://doi.org/10.1111/tmi.13741

Potential use of antibodies to provide an earlier indication of lymphatic filariasis resurgence in post-mass drug ad ministration surveillance in American Samoa.

Cadavid Restrepo, A., Gass, K., Won, K., Sheel, M., Robinson, K., Graves, P., Fuimaono, S., Lau, C.
09-02-2022
Int J Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35150913

Under the Global Programme to Eliminate Lymphatic Filariasis (LF), American Samoa conducted 7 rounds of mass drug administration (MDA) between 2000 and 2006. The territory passed transmission assessment surveys (TASs) in 2011 (TAS-1) and 2015 (TAS-2). In 2016, the territory failed TAS-3, indicating resurgence. This study aims to determine if antibodies (Abs) may have provided a timelier indication of LF resurgence in American Samoa. We examined school-level antigen (Ag) and Ab status (presence/absence of Ag- and Ab-positive children) and prevalence of single and combined Ab responses to Wb123, Bm14, and Bm33 Ags at each TAS. Pearson chi-square test and logistic regression were used to examine associations between school-level Ab prevalence in TAS-1 and TAS-2 and school-level Ag status in TAS-3. Schools with higher prevalence of Wb123 Ab in TAS-2 had higher odds of being Ag-positive in TAS-3 (odds ratio [OR] 24.5, 95% confidence interval [CI] 1.2-512.7). Schools that were Ab-positive for WB123 plus Bm14, Bm33, or both Bm14 and Bm33 in TAS-2 had higher odds of being Ag-positive in TAS-3 (OR 16.0-24.5). Abs could provide earlier signals of resurgence and enable a timelier response. The promising role of Abs in surveillance after MDA and decision making should be further investigated in other settings.

Prevalence and risk factors for positive lymphatic filariasis antibody in Sabah, Malaysia: a cross-sectional study.

Zakaria, N., Avoi, R.
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Trans R Soc Trop Med Hyg
https://doi.org/10.1093/trstmh/trab132

Lymphatic filariasis (LF) is a public health problem in Sabah, Malaysia. In the subdistrict of Tangkarason, nine rounds of mass drug administration (MDA) were probably not effective in reducing the prevalence of microfilaria to the <1% threshold recommended by the World Health Organization for stopping MDA. This cross-sectional study was conducted to identify the risk factors associated with positive LF antibody in Tangkarason. Eligible adults >18 y of age in seven endemic villages in Tangkarason, Beluran, Sabah, were interviewed and tested for LF antibody using the Brugia Rapid kit. Multivariable logistic regression was employed to analyse the associated factors. A total of 244 respondents were included in this study. Their median age was 40 y (interquartile range 30-53). The antibody prevalence of brugian filariasis in the study population was 31.1% (95% confidence interval [CI] 25.7 to 37.2). Older age (adjusted odds ratio [aOR] 1.04 [95% CI 1.02 to 1.06]) and outdoor jobs (aOR 2.26 [95% CI 1.05 to 4.85]) were identified as independent risk factors for positive LF antibody. Participating in the MDA program previously (aOR 0.24 [95% CI 0.10 to 0.57]) was found to be a protective factor for LF infection. A high prevalence of microfilariae was confirmed in all the study sites, which was above the target of <1%. Important factors associated with positive LF antibody were identified, which could be used as a guide for program managers to design more focused control measures in LF-endemic areas.

Molecular evolution, binding site interpretation and functional divergence of aspartate semialdehyde dehydrogenase.

Amala, M., Richard, M., Saritha, P., Prabhu, D., Veerapandiyan, M., Surekha, K., Jeyakanthan, J.
23-11-2020
J Biomol Struct Dyn
https://doi.org/10.1080/07391102.2020.1846619

Aspartate Semialdehyde Dehydrogenase (ASDH) is an important enzyme essential for the viability of pathogenic microorganisms. ASDH is mainly involved in amino acid and cell wall biosynthesis of microorganisms, hence it is considered to be a promising target for drug design. This enzyme depicts similar mechanistic function in all microorganisms; although, the kinetic efficiency of an enzyme differs according to their active site residual composition. Therefore, understanding the residual variation and kinetic efficiency of the enzyme would pave new insights in structure-based drug discovery and a novel drug molecule against ASDH. Here, ASDH from *Wolbachia* endosymbiont of *Brugia malayi* is used as a prime enzyme to execute evolutionary studies. The phylogenetic analysis was opted to classify 400 sequences of ASDH enzymes based on their structure and electrostatic surfaces. Analysis resulted in 37 monophyletic clades of diverse pathogenic and non-pathogenic organisms. The representative structures of 37 ASDHs from different clades were further deciphered to structural homologues. These enzymes exhibited presence of more positively charged surfaces than negatively charged surfaces in the active site pocket which restrains evolutionary significance. Docking studies of $NADP^+$ with 37 enzymes reveals that site-specific

residual variation in the active site pocket modulates the binding affinity (ranges of -13 to -9 kcal/mol). Type-I and Type-II divergence studies show, no significant functional divergence among ASDH, but residual changes were found among the enzyme that modulates the biochemical characteristics and catalytic efficiency. The present study not only explores residual alteration and catalytic variability, it also aids in the design of species-specific inhibitors.Communicated by Ramaswamy H. Sarma.

MYCETOME

Diagnostic imaging of foot mycetomas: A report on two cases.

Bentaleb, D., Mahdar, I., Noureddine, L., Mellouki, A., Sabiri, M., Lembarki, G., Essodegui, F., Regragui, M.
29-03-2022
Radiol Case Rep
https://doi.org/10.1016/j.radcr.2022.02.081

Mycetomas caused by aerobic actinomycetes are called actinomycetomas. It is primarily localized in subcutaneous tissue but it can spread to different tissue planes including the skin, deep tissues and structures and eventually the bones. We report the cases of 2 patients referred for evaluation of soft tissue masses involving the foot. A 40-year-old male and a 25-year-old male, in both cases MRI was performed to assess the extension, which was later completed by a CT scan. MRI revealed a low intensity matrix that represents fibrosis containing multiple high intensity lesions corresponding to the mycetoma grains. Within some of the lesions a low-intensity focus was identified. This "dot-in-circle sign" on an MRI is a pathognomonic feature of mycetoma. The purpose of this work is to describe the characteristic MRI appearance of foot mycetoma.

Time versus tissue: Timely identification of *Scedosporium Rhinosinusitis* in a post-COVID-19 case by MALDI-TOF MS leading to successful management.

Rai, P., Singh, A., Anand, K., Singh, S., Tomar, K.
28-03-2022
Med J Armed Forces India
https://doi.org/10.1016/j.mjafi.2022.01.014

COVID-19 (Coronavirus Disease 2019), illness with associated comorbidities and corticosteroid therapy makes the host immunocompromised and prone to opportunistic microbial infections. As the world continues to struggle with the pandemic of COVID-19, an increase in cases of opportunistic fungal infections have been reported from all over the world during the second wave of COVID-19 like aspergillosis, mucormycosis, and candidiasis. *Scedosporium apiospermum* is an emerging pathogen that is usually associated with mycetoma, pulmonary infection, and central nervous infections. It has been rarely associated with fungal rhinosinusitis (FRS). In this study, a rare case of FRS caused by *S.apiospermum* in an immunocompromised post-Covid-19 diabetic woman is reported.

ONCHOCERCOSE

Onchocerca cervicalis: A survey into awareness and knowledge of the parasite amongst UK equine veterinarians.

Mansell, S., Behnke, M.
31-03-2022
J Equine Vet Sci
https://pubmed.ncbi.nlm.nih.gov/35367519

The nematode Onchocerca cervicalis is the most common causative agent of equine onchocerciasis; this condition is characterised by pruritus and dermatitis and is a differential diagnosis for insect bite hypersensitivity. Onchocerciasis is currently presumed of minor importance within the UK, however prevalence may increase if macrocyclic lactone use declines amid concerns about anthelmintic resistance in gastrointestinal nematodes. This survey aimed to establish O. cervicalis awareness and knowledge levels amongst UK equine veterinarians and to determine approximate numbers of UK horses affected with unresponsive cases of dermatoses, including insect bite hypersensitivity. An online survey was distributed to UK equine vets between December 2019 and February 2020. Of 88 respondents, 78% were aware of O. cervicalis, however 49% of these answered less than half the questions presented about the parasite's lifecycle correctly. Approximately 25% of insect bite hypersensitivity cases respondents saw were deemed unresponsive to standard treatments, 84% of respondents had not previously considered onchocerciasis as a differential diagnosis in such cases. Findings suggest knowledge of O. cervicalis amongst UK equine vets is lacking, highlighting a need to raise awareness and consideration of the parasite as a differential when investigating equine dermatoses.

A qPCR to quantify Wolbachia from few Onchocerca volvulus microfilariae as a surrogate for adult worm histology in clinical trials of antiwolbachial drugs.

Schlabe, S., Korir, P., Lämmer, C., Landmann, F., Dubben, B., Koschel, M., Albers, A., Debrah, L., Debrah, A., Hübner, M., Pfarr, K., Klarmann-Schulz, U., Hoerauf, A.
10-01-2022
Parasitol Res
https://doi.org/10.1007/s00436-021-07411-5

The filarial nematode Onchocerca volvulus causes onchocerciasis (river blindness), a neglected tropical disease

affecting 21 million people, mostly in Sub-Saharan Africa. Targeting the endosymbiont Wolbachia with antibiotics leads to permanent sterilization and killing of adult worms. The gold standard to assess Wolbachia depletion is the histological examination of adult worms in nodules beginning at 6 months post-treatment. However, nodules can only be used once, limiting the time points to monitor Wolbachia depletion. A diagnostic to longitudinally monitor Wolbachia depletion from microfilariae (MF) at more frequent intervals<6 months post-treatment would accelerate clinical trials of antiwolbachials. We developed a TaqMan qPCR amplifying the single-copy gene wOvftsZ to quantify Wolbachia from as few as one MF that had migrated from skin biopsies and compared quantification using circular and linearized plasmids or synthetic dsDNA (gBlock®). qPCR for MF from the rodent nematode Litomosoides sigmodontis was used to support the reproducibility and validate the principle. The qPCR using as few as 2 MF from O. volvulus and L. sigmodontis reproducibly quantified Wolbachia. Use of a linearized plasmid standard or synthesized dsDNA resulted in numbers of Wolbachia/MF congruent with biologically plausible estimates in O. volvulus and L. sigmodontis MF. The qPCR assay yielded a median of 48.8 (range 1.5-280.5) Wolbachia/O. volvulus MF. The qPCR is a sensitive tool for quantifying Wolbachia in a few MF from skin biopsies and allows for establishing the qPCR as a surrogate parameter for monitoring Wolbachia depletion in adult worms of new antiwolbachial candidates.

SCHISTOSOMIASE

Synthetic peptides derived from the Schistosoma mansoni secretory protein Sm16 induce contrasting responses in hepatic stellate cells.

Carson, J., Robinson, M., Ramm, G., Gobert, G.
03-04-2022
Exp Parasitol
https://pubmed.ncbi.nlm.nih.gov/35385714

Sm16 is a 16 KDa protein released by Schistosoma mansoni that modulates inflammatory responses in host cells. Sm16 is expressed by several life cycle stages of S. mansoni, including the egg stage. Schistosome eggs are known to provoke chronic schistosomiasis pathology, which involves the development of liver fibrosis. Hepatic stellate cells (HSCs), which are responsible for this fibrosis, are susceptible to immunomodulation by S. mansoni whole egg secretions. To define the effects of Sm16 exposure on HSCs, two synthetic peptide derivatives of Sm16, coined "KS-84" and "KS-66", were tested against LX-2 cells, an immortalised human HSC line, and RNA sequencing was used to assess the transcriptional changes induced by each peptide. In total, 78 and 798 genes were found to be significantly differentially expressed by KS-84 and KS-66 treatment, respectively. In silico pathway analysis of these genes revealed that KS-84 reduced LX-2 cell activation and fibrotic potential, whereas KS-66 increased both processes. Reduced transforming growth factor-β1 (TGF-β1) signalling was identified as a potential mechanism of KS-84-induced inhibition of LX-2 activation. Taken together, these findings indicate a potential role for Sm16 in combatting fibrotic liver disease.

Management and treatment of decompensated hepatic fibrosis and severe refractory Schistosoma mansoni ascites with transjugular intrahepatic portosystemic shunt.

Santo, M., Gryschek, R., Farias, A., Andraus, W., Carvalho, N., Leite, O., Castro, F., Cerri, G., Hypólitti, G., Carnevale, F., Assis, A.
04-04-2022
Rev Inst Med Trop Sao Paulo
https://pubmed.ncbi.nlm.nih.gov/35384957

This study aimed to report the first case of a patient with hepatosplenic schistosomiasis mansoni, refractory ascites and portal vein thrombosis treated with a transjugular intrahepatic portosystemic shunt (TIPS), at the Instituto de Radiologia, Hospital das Clinicas, Faculdade de Medicina, Universidade de Sao Paulo, Brazil. After the procedure, the patient recovered favorably and progressed with portal pressure reduction and no deterioration of the liver function. Endovascular shunt modification is a conservative medical approach that often helps in reducing symptoms significantly, making it a less invasive and a safer alternative to liver transplantation for the treatment of schistosomiasis with portal hypertension.

Lippia alba and Lippia gracilis essential oils affect the viability and oviposition of Schistosoma mansoni.

Gomes, D., Negrão-Corrêa, D., Miranda, G., Rodrigues, J., Guedes, T., de Lucca Junior, W., Sá Filho, J., Nizio, D., Blank, A., Feitosa, V., Dolabella, S.
30-03-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35364048

Schistosomiasis is a neglected tropical disease that affects millions of people around the world. Currently, the only drug available for the treatment of this disease is praziquantel, which has low efficacy against immature helminth stages and there are reports of drug resistance. In this study, the chemical composition and the in vitro effect of essential oils (EOs) and major compounds from Lippia gracilis and Lippia alba against schistosomula and adult Schistosoma mansoni worms were evaluated. Adult S. mansoni worms cultured for 8h in the presence of L. gracilis EO (50 and 100 µg/mL) or for 2h with its major compound, carvacrol (100 µg/mL), had a 100% reduction in viability. After interaction with L. alba EO (100µg/mL), there was a reduction of approximately 60% in the viability of adult worms after 24 hours of exposure; citral (50 and 100 µg/mL), its major compound, reduced the viability after 24 hours by more than 75%. Treatment of schistosomula

with 100 µg/mL of L. gracilis or L. alba EOs for 6h led to a reduction in parasite viability of 80% and 16% respectively. Both EOs and their major compounds significantly reduced the oviposition of adult worms exposed to a non-lethal concentration (5 µg/mL). In addition, morphological changes such as the destruction of the tegument and disorganization of the reproductive system of male and female worms were visualized. Both EOs showed low cytotoxicity at a concentration of 50 µg/mL. The results encourage further investigation of these plants as a potential source of bioactive compounds against S. mansoni.

Molecular characterization and functional analysis of Schistosoma mekongi neuroglobin homolog.

Phuphisut, O., Kobpornchai, P., Chusongsang, P., Limpanont, Y., Kanjanapruthipong, T., Ampawong, S., Reamtong, O., Adisakwattana, P.
29-03-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35364046

Schistosomes are blood-dwelling parasites that are constantly exposed to high-level oxidative stress arising from parasite-intrinsic and host defense mechanisms. To survive in their hosts, schistosomes require an antioxidant system to minimize with oxidative stress. Several schistosome antioxidant enzymes have been identified and have been suggested to play indispensable antioxidant roles for the parasite. In addition to antioxidant enzymes, non-enzymatic antioxidants including small molecules, peptides, and proteins have been identified and characterized. Neuroglobin (Ngb), a nervous system-specific heme-binding protein, has been classified as a non-enzymatic antioxidant and is capable of scavenging a variety of free radical species. The antioxidant activity of Ngb has been well-studied in humans. Ngb is involved in cellular oxygen homeostasis and reactive oxygen/nitrogen scavenging in the central and peripheral nervous systems, but its functions in schistosome parasites have not yet been characterized. In this study, we aimed to characterize the molecular properties and functions of Schistosoma mekongi Ngb (SmeNgb) using bioinformatic, biochemical, and molecular biology approaches. The amino acid sequence of Ngb was highly conserved among schistosomes as well as closely related trematodes. SmeNgb was abundantly localized in the gastrodermis, vitelline, and ovary of adult female S. mekongi worms as well as in the tegument of adult male worms. Assessment of antioxidant activity demonstrated that recombinant SmeNgb had Fe^{2+} chelating and hydrogen peroxide scavenging activities. Intriguingly, siRNA silencing of SmeNgb gene expression resulted in tegument pathology. Understanding the properties and functions of SmNgb will help in future development of effective treatments and vaccines against S. mekongi, other schistosome parasites, and other platyhelminths.

Comparative mitogenomics of freshwater snails of the genus Bulinus, obligatory vectors of Schistosoma haematobium, causative agent of human urogenital schistosomiasis.

Zhang, S., Bu, L., Lu, L., Babbitt, C., Adema, C., Loker, E.
30-03-2022
Sci Rep
https://doi.org/10.1038/s41598-022-09305-7

Among the snail genera most responsible for vectoring human-infecting schistosomes, Bulinus, Biomphalaria, and Oncomelania, the former is in many respects the most important. Bulinid snails host the most common human blood fluke, Schistosoma haematobium, responsible for approximately two-thirds of the estimated 237 million cases of schistosomiasis. They also support transmission of schistosomes to millions of domestic and wild animals. Nonetheless, our basic knowledge of the 37 Bulinus species remains incomplete, especially with respect to genome information, even including mitogenome sequences. We determined complete mitogenome sequences for Bulinus truncatus, B. nasutus, and B. ugandae, and three representatives of B. globosus from eastern, central, and western Kenya. A difference of the location of tRNA-Asp was found between mitogenomes from the three species of the Bulinus africanus group and B. truncatus. Phylogenetic analysis using partial cox1 sequences suggests that B. globosus is a complex comprised of multiple species. We also highlight the status of B. ugandae as a distinct species with unusual interactions with the S. haematobium group parasites deserving of additional investigation. We provide sequence data for potential development of genetic markers for specific or intraspecific Bulinus studies, help elucidate the relationships among Bulinus species, and suggest ways in which mitogenomes may help understand the complex interactions between Schistosoma and Bulinus snails and their relatives.

Cross-reactivity of glycan-reactive HIV-1 broadly neutralizing antibodies with parasite glycans.

Huettner, I., Krumm, S., Serna, S., Brzezicka, K., Monaco, S., Walpole, S., van Diepen, A., Allan, F., Hicks, T., Kimuda, S., Emery, A., IAVI Protocol C Investigators & The IAVI African HIV Research Network, Landais, E., Hokke, C., Angulo, J., Reichardt, N., Doores, K.
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Cell Rep
https://pubmed.ncbi.nlm.nih.gov/35354052

The HIV-1 Envelope glycoprotein (Env) is the sole target for broadly neutralizing antibodies (bnAbs). Env is heavily glycosylated with host-derived N-glycans, and many bnAbs bind to, or are dependent upon, Env glycans for neutralization. Although glycan-binding bnAbs are frequently detected in HIV-infected individuals, attempts to elicit them have been unsuccessful because of the poor immunogenicity of Env N-glycans. Here, we report cross-reactivity of glycan-binding bnAbs with self- and non-self N-glycans and glycoprotein

antigens from different life-stages of Schistosoma mansoni. Using the IAVI Protocol C HIV infection cohort, we examine the relationship between S. mansoni seropositivity and development of bnAbs targeting glycan-dependent epitopes. We show that the unmutated common ancestor of the N332/V3-specific bnAb lineage PCDN76, isolated from an HIV-infected donor with S. mansoni seropositivity, binds to S. mansoni cercariae while lacking reactivity to gp120. Overall, these results present a strategy for elicitation of glycan-reactive bnAbs which could be exploited in HIV-1 vaccine development.

[Potential of tropical diseases in Germany : Important pathogens in travelers and migrants].

Revue de littérature

Kreuels, B., Schmiedel, S.
04-03-2022
Internist (Berl)
https://doi.org/10.1007/s00108-022-01280-5

Gastrointestinal infections are among the most frequent imported diseases diagnosed in Germany in travelers or migrants from the tropics. Acute traveler's diarrhea is the most frequent illness in long-distance travelers and in high-risk areas (e.g. India, Mexico) around one third of all travelers suffer from diarrhea. Chronic diarrhea plays a role especially after longer stays abroad (> 4 weeks) and in migrants and is often caused by protozoa. Helminths are less frequently the causative agent of gastrointestinal complaints (diarrhea, nausea, abdominal pain). A worm infestation of the large and small intestines is often present but helminths can also affect the liver or lead to generalized symptoms of illness when larvae migrate. In principle, in the case of gastrointestinal complaints after exposure to the tropics, the possibility of an imported tropical endemic infectious disease must be considered and appropriate diagnostics initiated. For travelers returning from tropical countries other, sometimes life-threatening diseases, such as malaria, typhoid fever, rickettsiosis and viral hemorrhagic fever (VHF) can present with gastrointestinal symptoms and should never be overlooked.

Metabolic Profiling of *S*-praziquantel: Structure Elucidation Using the Crystalline Sponge Method in Combination with Mass Spectrometry and Nuclear Magnetic Resonance.

Rosenberger, L., Jenniches, J., von Essen, C., Khutia, A., Kühn, C., Marx, A., Georgi, K., Hirsch, A., Hartmann, R., Badolo, L.
03-02-2022
Drug Metab Dispos
https://doi.org/10.1124/dmd.121.000663

Praziquantel (PZQ) is the drug of choice for treatment of the neglected tropical disease schistosomiasis. Although the drug has been extensively used over several decades and its metabolism well studied (several oxidative metabolites are known from literature), the knowledge of the complete structure of some of its metabolites remains elusive. Conventional techniques, such as nuclear magnetic resonance or liquid chromatography mass spectrometry were used in the past to investigate phase I and phase II metabolites of PZQ. These techniques are either limited to provide the complete molecular structure (liquid chromatography mass spectrometry) or require large amount of sample material (NMR), which are not always available when *in vitro* systems are used for investigation of the metabolites. In this study, we describe new structures of *S*-PZQ metabolites generated *in vitro* from human liver microsomes using the crystalline sponge method. After chromatographic separation and purification of the oxidative metabolites, ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry analysis was conducted to narrow down the position of oxidation to a certain part of the molecule. To determine the exact position of hydroxylation, singe-crystal X-ray diffraction analysis of the crystalline sponges and absorbed analyte was used to identify the structure of *S*-PZQ and its metabolites. The crystalline sponge method allowed for complete structure elucidation of the known metabolites *S*-*trans*-4'-hydroxy-PZQ (M1), *S*-*cis*-4'-hydroxy-PZQ (M2) and *S*-/*R*-11b-hydroxy-PZQ (M6) as well as the unknown metabolites *S*-9-hydroxy-PZQ (M3) and *S*-7-hydroxy-*S*-PZQ (M4). For comparison of structural elucidation techniques, one metabolite (M3) was additionally analyzed using NMR. SIGNIFICANCE STATEMENT: The information content of the metabolic pathway of praziquantel is still limited. The crystalline sponge method allowed the complete structural elucidation of three known and two unknown metabolites of *S*-praziquantel, using only trace amounts of analyte material, as demonstrated in this study.

Corrigendum to "Rational approach to drug discovery for human schistosomiasis" [Int. J. Parasitol. Drugs Drug Resist. 16 (2021) 140-147].

LoVerde, P., Alwan, S., Taylor, A., Rhodes, J., Chevalier, F., Anderson, T., McHardy, S.
19-01-2022
Int J Parasitol Drugs Drug Resist
https://pubmed.ncbi.nlm.nih.gov/35067439

Bibliometric analysis of schistosomiasis research in Southeast Asia (1908-2020).

Tantengco, O., Rojo, R.
20-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35065014

This study determined the characteristics and trends of published articles regarding schistosomiasis in Southeast Asian countries through a bibliometric analysis. Using the Scopus database, we identified all original research articles on schistosomiasis from 1908 to 2020 from SEA countries: Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar,

Philippines, Singapore, Thailand, and Vietnam. Bibliographic and citation information was obtained, and visualization of collaboration networks of countries and keywords related to schistosomiasis was conducted using VOSviewer software. We obtained 528 schistosomiasis articles published between 1908 and 2020 from SEA countries. The number of publications continued to increase and peaked from 2000 until 2020. The Philippines had the highest number of publications (n = 231), followed by Thailand (n = 153), and Malaysia (n = 64). The leading journals with the highest number of publications in this field include the Southeast Asian Journal of Tropical Medicine and Public Health (n = 96), Acta Tropica (n = 27), and Plos Neglected Tropical Diseases (n = 24). The most common keywords related to schistosomiasis research in SEA were "schistosomiasis", "Schistosoma japonicum", "Schistosoma mekongi", "Schistosoma mansoni", and "praziquantel". International collaboration was significantly correlated with scientific productivity for schistosomiasis research. Our study showed the research landscape, trends and development, and collaboration among researchers in schistosomiasis in SEA. Our results also revealed the limited schistosomiasis research in several SEA countries. There is a need for more research to improve our understanding of the epidemiology of schistosomiasis in SEA, which can help in improving the control and prevention of this disease.

Cobblestone Sign as an Unusual Manifestation of Colonic Schistosomiasis.

Huang, X., Huang, L., Xiao, Z.
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Am J Gastroenterol
https://doi.org/10.14309/ajg.0000000000001645

Schistosomiasis in Gabon from 2000 to 2021 - A review.

Revue de littérature

Dejon-Agobé, J., Edoa, J., Adegnika, A., Grobusch, M.
17-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35051384

Schistosomiasis is a public health issue of concern in Gabon, with the disease being reported from all regions of the country. The topic has been of interest for the local researchers and physicians for over two decades. The objective of this narrative review was to provide an overview of the research activities in the area from 2000 to early 2021. We performed a narrative literature review. The search strategy was designed to get a broad overview of the different research topics on schistosomiasis and the national control programme, and included grey literature. A total of 159 articles was screened, and 42 were included into the review in addition to the grey literature. During the past two decades, the work on schistosomiasis originated from five out of the nine provinces of the country, with diverse aspects of the disease investigated; including immunology, epidemiology, diagnosis and treatment. Several studies investigated various aspects of schistosomiasis-related morbidity in the respective study populations. The body of work demonstrates that much effort was made to understand the details of the host immune response to schistosomiasis, and the immune profile changes induced in patients treated with praziquantel. Although some MDA campaigns were conducted in the country; little, however, is known on the epidemiological situation of the disease, particularly of its distribution within the population, as well as co-infections with other parasitic diseases also endemic in the area. Progress has been made over the past two decades in the understanding of schistosomiasis in the country, including disease-related morbidity and its interaction with other parasitic infections, and the immunology and epidemiology of the disease. However, for optimising control of the disease, there is a need to fine-tune these findings with detailed local epidemiological and malacological data. We call for such studies to accomplish the knowledge of schistosomiasis in the country, particularly in areas of moderate or high endemicity, and recommend this approach to comparable schistosomiasis-endemic areas elsewhere.

Evaluation of loop-mediated isothermal amplification assay and enzyme-linked immunosorbent assay in detecting Schistosoma japonicum in Siargao Island, Surigao del Norte, the Philippines.

Belizario, V., Delos Trinos, J., Sison, O., Destura, R., Medina, J., Gigataras, A., Petronio-Santos, J., Abarientos, A.
14-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35038427

This study aimed to describe the prevalence and seroprevalence of schistosomiasis in Siargao Island, Surigao del Norte and to compare the performance of enzyme-linked immunosorbent assay antibody test (ELISA Ab) and loop-mediated isothermal amplification assay (LAMP) for diagnosis of schistosomiasis. The study was conducted in selected barangays (villages) in five municipalities in Siargao Island, Surigao del Norte and included school-age children (SAC) who submitted stool and blood samples. Stool samples were examined using the Kato-Katz technique. Blood samples were collected through venipuncture. The stool samples and the blood samples collected were tested using LAMP assay and polymerase chain reaction (PCR). The blood samples were examined using ELISA Ab. Diagnostic performance of LAMP assay using stool specimen was evaluated using Kato-Katz technique and PCR assay as the composite reference standard, while PCR assay was used as the reference standard to evaluate LAMP assay and ELISA Ab using blood specimens. A total of 417 stool samples from SAC were examined. The prevalence of schistosomiasis and moderate-heavy intensity (MHI) schistosomiasis were 3.8% and 1.4%, respectively. Schistosomiasis and soil-transmitted helminthiases (STH) coinfection prevalence were 2.6%. A total of 425 blood samples were examined using ELISA Ab. Seroprevalence was

61.6%. The municipality of San Isidro had the highest seroprevalence at 84.8%, while Burgos had the lowest seroprevalence at 48.5%.LAMP assay had higher sensitivity and positive predictive value but lower specificity when using stool than when using blood samples. Its negative predictive value was similar regardless of the specimen used. ELISA Ab has higher sensitivity and negative predictive value than LAMP assay although it has lower specificity and positive predictive value. This may be due to ELISA Ab measuring Schistosoma exposure and is thus unable to distinguish past from active infection. Schistosomiasis remains a public health concern in Siargao Island, Surigao del Norte. The locally developed LAMP assay offers a simpler diagnostic test for schistosomiasis compared with PCR, while minimizing the risk of misdiagnosis compared with Kato-Katz technique. It could serve as a point of care diagnostics for schistosomiasis. ELISA Ab is more useful in surveillance particularly in low-endemicity areas where determination of exposure is more important than differentiating past from active infection. ELISA Ab may be helpful in the clinical setting when coupled with the expertise of a physician who is familiar with schistosomiasis.

Kidney injury biomarkers and parasitic loads of Schistosoma mansoni in a highly endemic area in northeastern Brazil.

Galvão, R., Meneses, G., Pinheiro, M., Martins, A., Daher, E., Bezerra, F.
14-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35038425

Schistosomiasis affects approximately 240 million people worldwide. In Brazil, it is estimated that 1.5 million people are infected with Schistosoma mansoni and up to 15% of diagnosed individuals develop kidney damage. Renal involvement in schistosomiasis mansoni is characterized by glomerular lesions, with a high incidence, especially in chronically infected patients living in areas of high endemicity. Renal damage occurs slowly and is often asymptomatic, with a long-term manifestation of chronic kidney disease, with progressive loss of kidney functions, and early detection of subclinical kidney disease is of great importance. The aim of this study was to investigate kidney damage in patients infected with S. mansoni through urinary biomarkers of kidney injury and their association with the different parasite loads found. The patients were divided into two groups based on the diagnosis of infection by S. mansoni by the Kato-Katz and IgG-ELISA-SEA method: group of individuals infected by S. mansoni, Kato-Katz positive (PG); and group of individuals not infected by S. mansoni, Kato-Katz-negative (NG). Urinary creatinine and albuminuria were determined by immunoturbidimetry and proteinuria by the colorimetric method. The urinary biomarkers of podocyte injury (VEGF and Nephrin) and glomerular inflammation (MCP-1) were quantified by immunoassay and expressed by the urinary creatinine ratio. Urinary VEGF showed significantly higher levels in PG compared to NG ($p = 0.004$), increasing at all intensities of infection including low parasite load ($p = 0.020$). Our results show increased signs of podocyte damage in patients with schistosomiasis mansoni regardless of the parasite load, evidenced by increased urinary VEGF levels. However, further studies are needed since data related to schistosomiasis glomerulopathy and its association with new urinary biomarkers of kidney injury are scarce in the literature.

Toxic, cytotoxic and genotoxic effect of saline extract and fraction of Parkia pendula seeds in the developmental stages of Biomphalaria glabrata (Say 1818 - intermediate host) and cercaricide activity against the infectious agent of schistosomiasis.

Batista, J., de Araújo, H., Aguiar, T., Ferreira, S., Lima, M., Pereira, D., Ferreira, M., Soares, L., Melo, A., Albuquerque, M., Aires, A., Coelho, L.
14-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35033504

This study describes for the first time the effect of saline extract and Parkia pendula seed fraction on Biomphalaria glabrata adult embryos and molluscs well as the reproductive parameters (fecundity and fertility) and survival, in addition to cytotoxicity and genotoxicity through the profile of blood cells after exposure to sublethal concentrations. Furthermore, we analyzed the action of both preparations against the cercariae of Schistosoma mansoni and their environmental safety using the bioindicator Artemia salina. The saline extract and fraction showed toxic effects for embryos (CL_{90} of 464.25, 479.62, 731.28, 643.28, 408.43 and 250.94, 318.03, 406.12, 635.64, 1.145 mg/mL, for blastula, gastrula, trocophore, veliger and hippo stage respectively), adult snails after 24 h of exposure (CL_{90} of 9.50 and 10.92 mg/mL, respectively) with increased mortality after 7 days of observation and significant decrease ($p < 0.05$; $p < 0.01$ and $p < 0.001$) in egg mass deposition. At sublethal concentrations, an increase in quantitative and morphological changes in hemocytes was observed, and in the genotoxicity/comet assay analysis, varying degrees of nuclear damage were detected. In addition, the saline extract showed changes in the motility of the cercariae, while the fraction howed toxicity from a concentration of 1.0 mg/mL. The saline extract showed toxicity to A. salina at the highest concentrations (3.0, 4.0 and 5.0 mg/mL), while the fraction did not show ecotoxicity. Thus, the saline extract and fraction was promising in combating schistosomiasis by eliminating the intermediate host and causing alterations and/or mortality to the infectious agent.

Comparative metabolic profiling by ^{1}H-NMR spectroscopy analysis reveals the adaptation of S. mansoni from its host to in vitro culture conditions: a pilot study with ex vivo and GSH-supplemented medium-cultured parasites.

Fustaino, V., Gimmelli, R., Guidi, A., Lentini, S., Saccoccia, F., Petrella, G., Cicero, D., Ruberti, G.
13-01-2022

Parasitol Res
https://doi.org/10.1007/s00436-022-07426-6

Schistosomiasis is a neglected tropical disease caused by parasitic flatworms (blood fluke) of the genus Schistosoma. Parasites acquire most nutrients for their development and sustainment within the definitive host either by ingestion into the gut or across the body surface. Over the years, the best conditions for long-term maintenance of parasites in vitro have been thoroughly established. In our hands, ^{1}H-NMR spectroscopy represents a powerful tool to characterize the metabolic changes in S. mansoni in response to culturing condition perturbations. In order to compare the metabolic fingerprint of ex vivo and parasites cultured in vitro with or without the supplement of reduced glutathione, we conducted a pilot study applying the ^{1}H-NMR spectroscopy-based metabolomics. We obtained new insight into specific metabolic pathways modulated under these different experimental conditions.

Calpain inhibitor suppresses both extracellular vesicle-mediated secretion of miRNAs and egg production from paired adults of Schistosoma japonicum.

Kumagai, T., Shimogawara, R., Ichimura, K., Iwanaga, S.
08-01-2022
Parasitol Int
https://pubmed.ncbi.nlm.nih.gov/35007765

Extracellular vesicles (EVs) have been reported to be secreted from Schistosoma japonicum at all developmental stages. However, the reproduction and communication mechanisms between the paired adults through the EVs in dioecious Trematoda have not been reported. In this study, EVs containing many exosome-like vesicles and microvesicles were observed in the supernatants of paired adults cultured in vitro, and abundant selected miRNAs were contained in them. In particular, the female-specific miR-bantam was present only in vesicles and was hardly secreted outside the vesicles. In this study, we found that male-female pairing induced secretion of miR-3479 and miR-bantam in EVs, but not of male-specific miR-61. Furthermore, ingestion of mouse erythrocytes also increased the production of miRNAs in paired adult and single female worms. Vesicles were found in the tegument of females treated with erythrocytes under electron microscopy. After the paired worms were treated with several inhibitors against the secretion of EVs, only calpain inhibitor (calpeptin) significantly reduced the amount of miRNA in EVs. Furthermore, the worms treated with only calpeptin inhibited egg production in vitro. Together, these results indicate that qualitative miRNA production through EVs regulated by calpain plays a role in egg production in S. japonicum.

Resolution of systemic complications in Schistosoma mansoni-infected mice by concomitant treatment with praziquantel and Schisandrin B.

Lam, H., Cheng, P., Peng, S.
04-12-2021
Int J Parasitol
https://pubmed.ncbi.nlm.nih.gov/34875254

Schistosomiasis is a tropical parasitic disease, in which the major clinical manifestation includes hepatosplenomegaly, portal hypertension, and organs fibrosis. Clinically, treatment of schistosomiasis involves the use of praziquantel (PZQ) and supportive care, which does not improve the patient's outcome as liver injuries persist. Here we show the beneficial effects of using PZQ in combination with Schisandrin B (Sch B). Concomitant treatment with PZQ and Sch B resulted in a significant improvement of hepatosplenomegaly and fibrosis, compared with single-agent treatment. We also demonstrated that PZQ-Sch B treatment ameliorates injuries in the lungs and intestine better than the sole use of PZQ or Sch B. In addition, PZQ-Sch B treatment improves the survival of S. mansoni-infected mice, and the treatment combination yields better therapeutic outcomes, as indicated by a partial improvement in neurological function. These results were accompanied by a reduction in neurological injuries. Collectively, we suggest that PZQ-Sch B concomitant therapy may be useful to alleviate schistosomiasis-associated liver injuries and prevent systemic complications.

Long non-coding RNAs as possible therapeutic targets in protozoa, and in Schistosoma and other helminths.

Revue de littérature

Silveira, G., Coelho, H., Amaral, M., Verjovski-Almeida, S.
03-12-2021
Parasitol Res
https://doi.org/10.1007/s00436-021-07384-5

Long non-coding RNAs (lncRNAs) emerged in the past 20 years due to massive amounts of scientific data regarding transcriptomic analyses. They have been implicated in a plethora of cellular processes in higher eukaryotes. However, little is known about lncRNA possible involvement in parasitic diseases, with most studies only detecting their presence in parasites of human medical importance. Here, we review the progress on lncRNA studies and their functions in protozoans and helminths. In addition, we show an example of knockdown of one lncRNA in Schistosoma mansoni, SmLINC156349, which led to in vitro parasite adhesion, motility, and pairing impairment, with a 20% decrease in parasite viability and 33% reduction in female oviposition. Other observed phenotypes were a decrease in the proliferation rate of both male and female worms and their gonads, and reduced female lipid and vitelline droplets that are markers for well-developed vitellaria. Impairment of female worms' vitellaria in SmLINC156349-silenced worms led to egg development deficiency. All those results demonstrate the great potential of the tools and methods to characterize lncRNAs as potential new therapeutic targets. Further, we discuss the challenges and limitations of current methods for studying lncRNAs in parasites and possible solutions to overcome them, and we highlight the future directions of this

exciting field.

Discovery of novel antischistosomal scaffolds from the open access Pandemic Response Box.

Biendl, S., Häberli, C., Keiser, J.
19-10-2021
Expert Rev Anti Infect Ther
https://doi.org/10.1080/14787210.2022.1990042

Treatment and control of schistosomiasis rely on a single drug, praziquantel. New orally active antischistosomals featuring novel molecular scaffolds are urgently needed to prevent the emergence of resistance. We screened 400 drug-like compounds contained in the open-access Pandemic Response Box (PRB) against newly transformed schistosomula (NTS) at a concentration of 10 µM scoring death, changes in motility, and morphological alterations. Compounds displaying an activity ≥66% at 72 h underwent testing against adult *Schistosoma mansoni in vitro*. Fast-acting (≥66% at 24 h), nontoxic drugs focusing on late-stage and approved drugs were investigated in the patent *S. mansoni* mouse model. We identified 26 hits active against NTS, of which 17 elicited ≥66% activity against adult *S. mansoni* following 24 h of drug exposure. The highest activity against *adult S. mansoni* was observed with MMV1581558 (EC_{50} value of 0.18 ± 0.01 µM) and nitazoxanide (0.47 ± 0.07 µM). Of the five compounds tested *in vivo*, MMV1581558 and the approved drug ozanimod reduced average worm burden versus controls by 42 % and 36 %, respectively, after a single oral dose of 200 mg/kg bodyweight in mice harboring a chronic *S. mansoni* infection. MMV1581558 discovered from screening the PRB represents a novel antischistosomal scaffold with high *in vitro* antischistosomal activity amenable to chemical modification for drug development.

Rectal Bleeding in a 28-Year-Old Liberian Woman.

Mathias, R., Tse, E.
28-07-2021
Gastroenterology
https://pubmed.ncbi.nlm.nih.gov/34331915

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

Current status of intestinal parasitosis among patients attending teaching hospitals in Zagazig district, Northeastern Egypt.

Omar, M., Abdelal, H.
01-04-2022
Parasitol Res
https://doi.org/10.1007/s00436-022-07500-z

Almost 80% of health problems in the developing world are due to malnutrition and infectious diseases, which are mainly parasitic. Updated records on the prevalence of parasitic infections and the potential risk factors are essential to enhancing control strategies. Therefore, this study was conducted to evaluate the current situation of intestinal parasitism among patients attending teaching hospitals in Zagazig district, Northeastern Egypt. The study involved five hundred cases. They were all subjected to faecal examination using direct smear measure and two commercial faecal concentrators: Mini-Parasep® solvent-free and Mini-FLOTAC procedures. Mini-FLOTAC was performed with two solutions (FS2: saturated sodium chloride and FS7: zinc sulphate). The overall prevalence of intestinal parasitic infections was 56%. Different species were identified, like Giardia lamblia (12.6%), Entamoeba histolytica/dispar (10%), Ascaris lumbricoides (8.8%) and Hymenolepis nana (8.6%). Data analyses revealed a significant association of intestinal parasitism with different socio-demographic features of the participants. Our results showed a better diagnostic performance of Mini-Parasep® in the overall recovery of intestinal parasites. It was more accurate than Mini-FLOTAC in diagnosing both helminths and protozoan infections. Mini-FLOTAC (FS2) exhibited a higher sensitivity than FS7 for helminth recovery (74.6% vs 53.4%), while FS7 was more sensitive for protozoan infections (50.6% vs 43.8%). Intestinal parasitosis remains a challenging health problem in Zagazig city, wherever reliable diagnostic approaches are limited. Thus, our study has proposed the value of the commercial concentrators (Mini-Parasep® and Mini-FLOTAC) as alternative techniques for diagnosing a large variety of parasite species in resource-constrained settings.

GALE

Bullous Scabies in an Immunocompromised Host.

Wester, J., Jackson, L., Mokgosi, K., Barak, T., Hazeem, M.
28-03-2022
Case Rep Infect Dis
https://doi.org/10.1155/2022/3797745

A 40-year-old woman with a history of poorly controlled HIV presented to a district referral hospital in rural Botswana for a generalized skin rash of several months duration. The highly pruritic rash predominantly involved her hands and feet and was associated with bullae that were present for days at a time before rupturing without drainage or discharge. The patient endorsed night sweats, periodic fevers, occasional cough productive of blood-tinged sputum, fatigue, and weight loss. On admission, CD4 count was 46 cells/mm^3 and viral load was >750000 copies/mL. Pulmonary tuberculosis testing via sputum was negative twice. A blood count demonstrated eosinophilia. Oral acyclovir was started empirically for disseminated herpes virus infection, with topical

beclomethasone and intravenous antibiotics for possible superinfected bullous dermatosis. With inadequate response to treatment, a skin biopsy was obtained and microscopic examination demonstrated scabies mites. The absence of skin burrows, the presence of bullae, and working in a low-resource setting without direct access to microscopic examination delayed diagnosis. The patient was initiated on topical permethrin. Oral ivermectin was not available in country and was obtained from overseas shipment, delaying treatment initiation. Drastic improvement was seen after the patient initiated ivermectin. A local nurse in the patient's village visited her community and found multiple individuals with active scabies infection. The patient's discharge was delayed until these community members were treated successfully with topical permethrin. This case describes an atypical presentation of scabies in an under-resourced setting, demonstrating unique diagnostic, therapeutic, and public health challenges.

Development of a nucleic acid-based lateral flow assay to diagnose ordinary scabies.

Chun, E., Kim, J., Yang, S., Kim, S., Kim, C.
20-11-2021
J Eur Acad Dermatol Venereol
https://doi.org/10.1111/jdv.17810

A prospective cohort of patients with common scabies treated with 10% benzyl benzoate emulsion as monotherapy: EPIGALE study.

Caumes, E., Marty, M., Cadot, M., Boulanger, P., Rousseaux, C., Petit, A.
12-09-2021
Int J Dermatol
https://doi.org/10.1111/ijd.15879

In addition to general measures, pharmacological treatment is the basis of the management of scabies. No recent data in real-life are available on the efficacy and safety of 10% benzyl benzoate emulsion for skin application administered as monotherapy. This prospective, multicenter, French observational study comprised a registry and a prospective cohort with a follow-up at 28 days and a telephone call at week 12. To participate in the registry, patients had to be over 1 month old, ambulatory, presenting common, nonhyperkeratotic, untreated scabies. To be included in the cohort, patients had to be included in the registry and treated with two applications of 10% benzyl benzoate emulsion 8 days apart. The primary endpoint was cure at day 28. Of the 186 patients included in the registry, 116 were included in the cohort. Fourteen patients were included in the cohort without being included in the registry, which led to a total of 130 patients in the cohort. At day 28, 119/130 (91.5%; 95% CI 85.4-95.6%) were clinically cured. The cure was confirmed by dermoscopy in 44/47 patients (93%). Among the 130 patients, the cure rate was 82% at week 12. Of the 119 patients cured at day 28, the rate of cure at week 12 was 89.9%. In real life, two applications of 10% benzyl benzoate emulsion 8 days apart provides high cure rates in patients with common scabies.

MORSURES DE SERPENT

Use of geospatial analyses to address snakebite hotspots in mid-northern Brazil - A direction to health planning in shortfall biodiversity knowledge areas.

Melo Araújo, S., Ceron, K., Guedes, T.
04-04-2022
Toxicon
https://pubmed.ncbi.nlm.nih.gov/35390425

Knowing the distribution of venomous snakes of medical importance is essential to identify areas at risk for snakebites. Thus, we used an integrative approach based on the application of geographic distribution data of venomous snakes, species distribution modeling (SDM), spatial organization of snakebites, and information on human population density for mapping the potential distribution of snakes and identifying areas at risk of snakebites in the state of Maranhão (mid-northern Brazil). From a compiled a database of venomous snake records deposited in biological collections and the literature, we predict the potential distribution of venomous snakes in Maranhão, a state whose diversity and geographic distribution of venomous snake species are poorly known. With this, we constructed potential distribution maps for each venomous snake species with at least one occurrence record within state boundaries, as well as generalized maps by family (Viperidae and Elapidae) and the total number of venomous snakes in Maranhão State. We also obtained data on the number of snakebites recorded in each municipality of Maranhão over a decade (2009-2019) and we ran a Generalized Linear Model to test for relationships between the number of venomous snakebites, the area of occurrence of snakes, and human population density. We obtained 1046 records of venomous snake species for Maranhão, represented by 17 viperid and elapid species. Most of the records were from Viperidae (mostly Bothrops atrox and B. marajoensis) and were concentrated mainly in the Amazonia of the northern portion of the state. The models showed accurate predictive performance for all modeled species. The entire area of Maranhão exhibits environmental conditions for the occurrence of venomous snakes, with higher suitability indices in the northern region, in the Amazon rainforest. The number of snakebites was positively correlated with high-risk areas (i.e., greater distribution of venomous snakes) and human population density. Our study is a pioneer in using species distribution modeling in mid-northern Brazil to address the scarcity of data on snakebite-causing species, directly contributing to the theme of neglected tropical diseases of the World Health

Organization.

Comment on "Crotalidae Polyvalent Immune Fab and Cost-Effective Management of Hospital Admissions for Snakebites".

Mullins, M., Schwarz, E., Liss, D., Devgun, J., Baumgartner, K.
03-04-2022
Am Surg
https://doi.org/10.1177/00031348221078965

Isolated Ptosis Following a Vipera aspis Bite.

Blasco Mariño, R., Soteras Martínez, I., Hernandez Roca, A., Zafren, K.
30-03-2022
Wilderness Environ Med
https://pubmed.ncbi.nlm.nih.gov/35367125

In Spain, snakebites are uncommon medical emergencies that cause barely 100 hospitalizations annually. Most of the venomous bites are by snakes of the Viperidae family. Venom from Vipera snakes is reported to have cytotoxic and hematotoxic effects, and neurological effects have also been described. Ptosis (cranial nerve III palsy) is the most common sign, although any cranial nerve can be affected. We describe isolated ptosis, which was very likely after a Vipera aspis bite in the East Catalonian Pyrenees. No antivenom was administered. The ptosis resolved spontaneously within 10 h. Although neurologic findings are usually mild, they indicate a moderate or severe envenomation. Treating snakebites can be challenging for clinicians, especially when there are uncommon clinical manifestations. A toxicologist at a poison center should be consulted to help guide management. Development of local protocols may provide clinical support.

Lower levels of CXCL-8 and IL-2 on admission as predictors of early adverse reactions to Bothrops antivenom in the Brazilian Amazon.

Soares, F., Ibiapina, H., Sartim, M., Mendonça-da-Silva, I., Nascimento, E., Ferreira, L., Cerni, F., Malheiro, A., Pucca, M., Wen, F., Maria Moura-da-Silva, A., Costa, A., Monteiro, W., Sachett, J.
12-02-2022
Cytokine
https://pubmed.ncbi.nlm.nih.gov/35168182

Snakebite envenomings are considered a global health problem. The specific therapy for these envenomings consists of administering animal-derived antivenoms aiming to neutralize the venom toxins. Antivenoms have been used effectively to treat snakebites for more than a century; however, their administration may result in early and/or late adverse reactions. The present study presents the prevalence of early adverse reactions (EARs) towards Bothrops antivenom therapy in a health tertiary unit in the Brazilian Amazon and explores if specific plasma cytokines and chemokines from envenomed patients could be used as predictors of EARs. A cohort of patients bitten by Bothrops atrox was followed-up at the Fundação de Medicina Tropical Dr. Heitor Vieira Dourado (FMT-HVD), from 2014 to 2016. Patients were treated with the Brazilian Bothrops antivenom and CXCL-8, CCL-5, CXCL-9, CCL-2, CXCL-10, IL-6, TNF, IL-2, IL-10, IFN-γ, IL-4, and IL-17A were evaluated in patients' plasma samples before and after antivenom administration. From the total of patients (n = 186), mostly were male (82.3%), inhabiting rural areas (87.1%), with an average age of 35 years. Most of the patients (83.8%) were admitted to the hospital within 6 h after the accident, 26 (14%) reported having suffered a previous snakebite, and 97 (52.1%) received between 7 and 9 antivenom vials. The frequency of antivenom-induced EARs was 11.8% (22), resulting mostly of mild reactions. Urticaria was the major EAR manifestation (46.4%). Interestingly, CXCL-8 and IL-2 showed significantly lower levels in patients who progressed to EARs, although IL-2 levels might not represent biological relevance due the small magnitude difference between groups. This study reveals that CXCL-8 and IL-2 could play a role in the onset of EARs in pit viper envenomings.

First step in assessment of VipGrade®, a computerized clinical decision system to assess *Vipera* envenomation grading: a single-center interrater reliability study.

Boels, D., Courtois, A., Paradis, C., Caillet, P., Labadie, M.
28-10-2021
Clin Toxicol (Phila)
https://doi.org/10.1080/15563650.2021.1993241

We conducted a retrospective review of *Vipera* spp. snakebite cases registered by the PCC of Bordeaux, France, between January 1, 2018, and December 31, 2020, evaluating the agreement between VipGrade® assessments, toxicologists' assessments, and current guidelines. 133 patients with *Vipera aspis* snakebites were included. There was 100% agreement in severity grading by PCC guidelines and VipGrade®. However, grading by toxicologists and VipGrade® diverged in 19 cases (85% agreement; κ=0.80; 95% CI: 0.71 to 0.87). The VipGrade® tool's grading reflects current PCC guidelines, which are authoritative in France, and may allow for a more rapid and standardized determination of management and follow-up of viper-bitten patients. It should be noted, however, that the more complex and dynamic aspects of management are not included in VipGrade®. Its purpose is to supplement, not replace, the advice of the PCC's clinical toxicologists, and this advice should be sought whenever a viper bite is encountered in clinical practice.