Réseau MTN Francophone

Veille scientifique
Maladies tropicales négligées

Semaine 17

25 avril 2022 – 02 mai 2022

DENGUE, CHIKUNGUNYA ET MALADIE A VIRUS ZIKA

Beneath the surface: Amino acid variation underlying two decades of dengue virus antigenic dynamics in Bangkok, Thailand.

Huang, A., Salje, H., Escoto, A., Chowdhury, N., Chávez, C., Garcia-Carreras, B., Rutvisuttinunt, W., Maljkovic Berry, I., Gromowski, G., Wang, L., Klungthong, C., Thaisomboonsuk, B., Nisalak, A., Trimmer-Smith, L., Rodriguez-Barraquer, I., Ellison, D., Jones, A., Fernandez, S., Thomas, S., Smith, D., Jarman, R., Whitehead, S., Cummings, D., Katzelnick, L.
02-05-2022
PLoS Pathog
https://doi.org/10.1371/journal.ppat.1010500

Neutralizing antibodies are important correlates of protection against dengue. Yet, determinants of variation in neutralization across strains within the four dengue virus serotypes (DENV1-4) is imperfectly understood. Studies focus on structural DENV proteins, especially the envelope (E), the primary target of anti-DENV antibodies. Although changes in immune recognition (antigenicity) are often attributed to variation in epitope residues, viral processes influencing conformation and epitope accessibility also affect neutralizability, suggesting possible modulating roles of nonstructural proteins. We estimated effects of residue changes in all 10 DENV proteins on antigenic distances between 348 DENV collected from individuals living in Bangkok, Thailand (1994-2014). Antigenic distances were derived from response of each virus to a panel of twenty non-human primate antisera. Across 100 estimations, excluding 10% of virus pairs each time, 77 of 295 positions with residue variability in E consistently conferred antigenic effects; 52 were within ±3 sites of known binding sites of neutralizing human monoclonal antibodies, exceeding expectations from random assignments of effects to sites ($p = 0.037$). Effects were also identified for 16 sites on the stem/anchor of E which were only recently shown to become exposed under physiological conditions. For all proteins, except nonstructural protein 2A (NS2A), root-mean-squared-error (RMSE) in predicting distances between pairs held out in each estimation did not outperform sequences of equal length derived from all proteins or E, suggesting that antigenic signals present were likely through linkage with E. Adjusted for E, we identified 62/219 sites embedding the excess signals in NS2A. Concatenating these sites to E additionally explained 3.4% to 4.0% of observed variance in antigenic distances from when E alone (50.5% to 50.8%); RMSE outperformed concatenating E with sites from any protein of the virus (ΔRMSE, 95%IQR: 0.01, 0.05). Our results support examining antigenic determinants beyond the DENV surface.

Dengue fever as a reemerging disease in upper Egypt: Diagnosis, vector surveillance and genetic diversity using RT-LAMP assay.

Gaber, M., Ahmad, A., El-Kady, A., Tolba, M., Suzuki, Y., Mohammed, S., Elossily, N.
02-05-2022
PLoS One
https://doi.org/10.1371/journal.pone.0265760

Background: The recent increase in dengue virus (DENV) outbreaks and the absence of an effective vaccine have highlighted the importance of developing rapid and effective diagnostic surveillance tests and mosquito-based screening programs. To establish effective control measures for preventing future DENV transmission, the present study was established to identify the main mosquito vector involved in the dengue fever (DF) outbreak in Upper Egypt in 2016 and detect the diversity of dengue virus serotypes circulating in both humans and vectors. Methods: We investigated the prevalence of DENV infection and circulating serotypes in the sera of 51 humans clinically suspected of DF and 1800 field-collected Aedes aegypti adult female mosquitoes grouped into 36 pooled samples. Both DENV non-structural protein (NS1) immunochromatographic strip assay and loop-mediated isothermal amplification (LAMP) were used for screening. Results: Overall, the rate of DENV infection in both human sera and pooled mosquito homogenate was 33.3%, as revealed by rapid dipstick immunochromatographic analysis. However, higher detection rates were observed with RT-LAMP assay of 60.8% and 44.4% for humans and vector mosquitoes, respectively. DENV-1 was the most prevalent serotype in both populations. A combination of two, three, or even four circulating serotypes was found in 87.5% of total positive pooled mosquito samples and 83.87% of DENV-positive human sera. Conclusion: The study reinforces the evidence of the reemergence of Aedes aegypti in Upper Egypt, inducing an outbreak of DENV. Mosquito-based surveillance of DENV infection is important to elucidate the viral activity rate and define serotype diversity to understand the virus dynamics in the reinfested area. Up to our knowledge, this is the first report of serotyping of DENV infection in an outbreak in Egypt using RT-LAMP assay.

COVID-19 and Dengue co-epidemic during the second wave of the pandemic in Bangladesh: A double blow for an overburdened healthcare system.

Patwary, M., Haque, M., Bardhan, M., Rodriguez-Morales, A.
02-05-2022
Disaster Med Public Health Prep
https://doi.org/10.1017/dmp.2022.105

Identification of neo-andrographolide compound targeting NS1 Lys14: an important residue in NS1 activity driving dengue pathogenesis.

Elumalai, E., Suresh Kumar, M.
01-05-2022
J Biomol Struct Dyn
https://doi.org/10.1080/07391102.2022.2068073

Dengue virus is part of the flaviviruses that spread through the Aedes mosquito species and causes vascular leakage and multiple organ failure. The non-structural protein 1 (NS1) is involved in the replication of Dengue virus. The glycosylated dimeric and hexameric form of NS1 is the biologically active form. Therefore, in this study, the NS1 protein was modeled in dimeric form which is predominantly present inside the host cell. The dimeric model was validated and it was glycosylated at ASN130 and ASN207 with oligomannose. This model was simulated for 100 ns to retrieve the global minima structure. The andrographolide and its four derivatives were docked non-specifically against the dimeric glycosylated NS1 protein. The neo-andrographolide compound showed strong interactions with favorable binding energy of -8.2 kcal/mol and electrostatic binding affinity of -8.9 kcal/mol. All docked ligand-protein complexes were simulated for 100 ns. The molecular dynamics simulation analysis comprising of root mean square deviation and fluctuation, the radius of gyration, hydrogen bonding, potential energy, principal component analysis, SASA, DSSP, Free energy Landscape, MM-PBSA and Electrostatic binding affinity revealed about the stability of complex systems. These andrographolide and its derivatives was found to be interacting with Lys14 and this residue was reported as one of the important residues in NS1 activity. Among all compounds, the neo-andrographolide compound has the promising potential to inhibit the activity of the NS1 which is necessary for the Dengue virus replication. HighlightsThe dimeric NS1 protein structure was modeled and glycosylated at ASN130 and ASN 207 with Oligo-mannose.The minimized structure was used for molecular docking studies with andrographolide and its derivatives.The Lys14 residue is well interfered by all compounds but based on molecular dynamics and binding affinity studies, neo-andrographolide compound has the promising potential to inhibit the activity of the NS1.Communicated by Ramaswamy H. Sarma.

Infectious diseases and predominant travel-related syndromes among long-term expatriates living in low-and middle- income countries: a scoping review.

Revue de littérature

Kitro, A., Ngamprasertchai, T., Srithanaviboonchai, K.
01-05-2022
Trop Dis Travel Med Vaccines
https://doi.org/10.1186/s40794-022-00168-4

Introduction: Expatriates working in low-and middle-income countries have unique health problems. Migration leads not only to an increase in individual health risk but also a risk of global impact, such as pandemics. Expatriates with no prior experience living in tropical settings have expressed greatest concern about infectious diseases and appropriate peri-travel consultation is essential to expatriates. The objective of this review is to describe infections and travel-related syndromes among expatriates living in low-and middle-income countries. **Methods:** MEDLINE database since the year 2000 was searched for relevant literature. Search terms were "long-term travel", "expatriate", and "health problems". The additional references were obtained from hand-searching of selected articles. **Results:** Up to 80% of expatriates suffered from gastrointestinal problems followed by dermatologic problems (up to 40%), and febrile systemic infection/vector-borne/parasitic infection (up to 34%) Expatriates living in Southeast Asia were at risk of vector-borne diseases including dengue and non-Plasmodium falciparum (pf) malaria while expatriates living in South Asia had a high prevalence of acute and chronic diarrhea. Staying long-term in Africa was related to an elevated risk for pf malaria and gastrointestinal infection. In Latin America, dermatologic problems were commonly reported illnesses among expatriates. **Conclusion:** Certain health risks for expatriates who are going to depart to specific regions should be the focus of pre-travel consultation. Specific health preparations may reduce the risk of disease throughout their time abroad. Disease and symptom awareness is essential for screening, early diagnosis, and better health outcomes for ill-expatriates.

Swift synthesis of zinc oxide nanoparticles using unripe fruit extract of Pergularia daemia: An enhanced and eco-friendly control agent against Zika virus vector Aedes aegypti.

Ishwarya, R., Jayakumar, R., Govindan, T., Govindarajan, M., Alharbi, N., Kadaikunnan, S., Khaled, J., Nicoletti, M., Vaseeharan, B.
26-04-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35487294

In this study Pergularia daemia unripe fruits were used to synthesize zinc oxide nanoparticles (Pd-ZnONPs). UV-vis Spectroscopy detected the production of ZnONPs. XRD, FTIR, SEM, and TEM studies were used to characterize the synthesized Pd-ZnONPs. Aedes aegypti (Ae. aegypti) third instar larvae were analyzed to diverse concentrations of Pd-unripe fruit extract and Pd-ZnONPs for 24 hours to assess the larvicidal effect. Mortality was also detected in Ae. aegypti larvae under laboratory conditions, with corresponding LC_{50} and LC_{90} values of 11.11 and 21.20 µg/ml. As a result of this study, the levels of total proteins, esterases, acetylcholine esterase, and phosphatase enzymes in the third instar larvae of Ae. aegypti were significantly lower than the control. These findings suggest that Pd-ZnONPs could be used to suppress mosquito larval populations.

Bio-fabricated silver nanoparticles for controlling dengue and filaria vectors and their characterization, as well as toxicological risk assessment in aquatic mesocosms.

Mondal, A., Sen, K., Mondal, A., Mishra, D., Debnath, P., Mondal, N.
26-04-2022
Environ Res
https://pubmed.ncbi.nlm.nih.gov/35487260

The present study is focused on synthesis of silver nanoparticles from weeds and an assessment of their mosquito larvicidal efficacy. This study also presented the toxicological effects as well as the stability of these nanoparticles in aquatic mesocosms. The weed Digiteria sanguinallis was first time used for the synthesis of silver nanoparticles. The synthesized nanoparticles were characterized by various analytical techniques, such as UV-VIS, TEM, FESEM, EDX, XRD, FTIR, and zeta potential study. The result revealed that the nanoparticles are crystalline, spherical shape with band gap 2.44 eV, and average size 18 nm. The LC_{50} value of synthesized AgNPs were recorded as 7.47 and 6.31 mg/L at 24 h against Cx. quinquefasciatus and A. albopictus respectively. In contrast, larvicidal activity of weed extract was insignificant against two target species. In aquatic mesocosm study, AgNPs (LC_{50} dose) does not alter the nature of water parameters within experimental period. However only EC % and ORP were changes because of silver ion oxidation. In biochemical parameters, only stress enzymes for animal and plant species were moderately altered under long term exposure. But glycogen, protein, and AchE of two mosquito species were significantly changed under same mesocosm setup within short exposure. Comparatively, in control mesocosm, synthesized AgNPs are naturally change their nano form within 20 days with the presence of all non-target species and pond sediment. Therefore, it can be concluded that biosynthesized AgNPs could be used as a larvicidal agent in near future with negligible effects on aquatic organisms.

Combined detection of molecular and serological signatures of viral infections: The dual assay concept.

Albuquerque, D., Martins, V., Fernandes, E., Zé-Zé, L., Alves, M., Cardoso, S.
25-04-2022
Biosens Bioelectron
https://pubmed.ncbi.nlm.nih.gov/35487137

The recent worldwide spread of viral infections has highlighted the need for accurate, fast, and inexpensive disease diagnosis and monitorization methods. Current diagnostics tend to focus either on molecular or serological testing. In this work we propose a dual detection assay approach for viral diseases, where both serological and molecular assays are combined in a single analysis performed on a magnetoresistive system. This type of assay guarantees an accurate assessment of the infection phase, saving time and costs associated with multiple independent tests. Zika and dengue viruses were used as model diseases for the validation of the system. Human IgG anti-zika and anti-dengue antibodies were successfully detected in infected patients' serum, using a novel approach combining competitive and sandwich strategies in a magnetoresistive portable platform. Specificity and sensitivity values of 100% were obtained. Calibration curves with dynamic ranges between 10 ng/mL and 1 µg/mL were established achieving LODs of 1.26 and 1.38 nM for IgG anti-ZIKV and anti-DENV antibodies, respectively. Viral RNA detection down to a few hundreds of pM was also successfully carried out after the design of specific oligo probes and primers for RT-PCR amplification. Dual assays were performed for both viruses, where viral RNA and anti-virus antibodies in serum samples were simultaneously detected. The results obtained for the detection of the molecular and serological targets in the dual assay format show no significant difference between the ones obtained individually, proving the feasibility and accuracy of the dual detection assay. This assay format represents a new paradigm in viral infections diagnostics.

Level of dengue preventive practices and associated factors in a Malaysian residential area during the COVID-19 pandemic: A cross-sectional study.

Mashudi, D., Ahmad, N., Mohd Said, S.
29-04-2022
PLoS One
https://doi.org/10.1371/journal.pone.0267899

Background: Dengue fever is a mosquito-borne viral infection that is endemic in more than 100 countries and has the highest incidence among infectious diseases in Malaysia. The increase of dengue fever cases during the COVID-19 pandemic and the movement control order (MCO) highlighted the necessity to assess the dengue preventive practices among the population. Thus, this study aimed to determine the level of dengue preventive practices and its associated factors among residents in a residential area in Johor, Malaysia during the COVID-19 pandemic. Method: A community-based cross-sectional study was conducted on 303 respondents from a Johor residential area between May and June 2021. A validated self-administered questionnaire was created using google forms and distributed to the respondents via WhatsApp. The questionnaire consisted of three sections: (i) Sociodemographic characteristics and history of dengue fever, (ii) dengue preventive practices, and (iii) six constructs of the Health Belief Model (HBM). The association between the dependent and independent variables were examined using multiple logistic regression with a significant level set at less than 0.05. Result: About half of the respondents have a good level of dengue preventive practices. Respondents with a history of dengue fever (aOR = 2.1, 95% CI: 1.1-4.2, p = 0.033), low perceived susceptibility (aOR = 1.8, 95% CI: 1.1-3.0, p = 0.018), high self-efficacy (aOR = 1.7, 95% CI: 1.0-2.8, p = 0.045), and high cues to take action (aOR = 2.5, 95% CI: 1.5-4.2, p < 0.001) had higher odds of practicing good dengue preventive measures. Conclusion: This study demonstrated a moderate level of dengue preventive practices during the COVID-19 pandemic. Therefore, a stronger dengue control programme is recommended by focusing on cues to take action, self-efficacy, and recruiting those with a history of dengue fever to assist health authorities in promoting good dengue preventive practices in the community.

Human Seroprevalence for Dengue, Ross River, and Barmah Forest viruses in Australia and the Pacific: A systematic review spanning seven decades.

Madzokere, E., Qian, W., Webster, J., Walker, D., Lim, E., Harley, D., Herrero, L.
29-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010314

Background: Dengue (DENV), Ross River (RRV) and Barmah Forest viruses (BFV) are the most common human arboviral infections in Australia and the Pacific Island Countries and Territories (PICTs) and are associated with debilitating symptoms. All are nationally notifiable in Australia, but routine surveillance is limited to a few locations in the PICTs. Understanding the level of human exposure to these viruses can inform disease management and mitigation strategies. To assess the historic and current seroprevalence of DENV, RRV and BFV in Australia and the PICTs we conducted a systematic literature review of all published quantitative serosurveys. **Methodology and principal findings:** The Preferred Reporting of Items for Systematic Reviews and Meta-Analyses procedures were adopted to produce a protocol to systematically search for published studies reporting the seroprevalence of DENV, RRV and BFV in Australia and the PICTs. Data for author, research year, location, study population, serosurvey methods and positive tests were extracted. A total of 41 papers, reporting 78 serosurveys of DENV, RRV and BFV including 62,327 samples met the inclusion criteria for this review. Seroprevalence varied depending on the assay used, strategy of sample collection and location of the study population. Significant differences were observed in reported seropositivity depending on the sample collection strategy with clinically targeted sampling reporting the highest seroprevalence across all three viruses. Non-stratified seroprevalence showed wide ranges in reported positivity with DENV 0.0% -95.6%, RRV 0.0%-100.0%, and BFV 0.3% to 12.5%. We discuss some of the causes of variation including serological methods used, selection bias in sample collection including clinical or environmental associations, and location of study site. We consider the extent to which serosurveys reflect the epidemiology of the viruses and provide broad recommendations regarding the conduct and reporting of arbovirus serosurveys. **Conclusions and significance:** Human serosurveys provide important information on the extent of human exposure to arboviruses across: (1) time, (2) place, and (3) person (e.g., age, gender, clinical presentation etc). Interpreting results obtained at these scales has the potential to inform us about transmission cycles, improve diagnostic surveillance, and mitigate future outbreaks. Future research should streamline methods and reduce bias to allow a better understanding of the burden of these diseases and the factors associated with seroprevalence. Greater consideration should be given to the interpretation of seroprevalence in studies, and increased rigour applied in linking seroprevalence to transmission dynamics.

Therapeutic efficacy of humanized monoclonal antibodies targeting dengue virus nonstructural protein 1 in the mouse model.

Tien, S., Chang, P., Lai, Y., Chuang, Y., Tseng, C., Kao, Y., Huang, H., Hsiao, Y., Liu, Y., Lin, H., Chu, C., Cheng, M., Ho, T., Chang, C., Ko, S., Shen, C., Anderson, R., Lin, Y., Wan, S., Yeh, T.
29-04-2022
PLoS Pathog
https://doi.org/10.1371/journal.ppat.1010469

Dengue virus (DENV) which infects about 390 million people per year in tropical and subtropical areas manifests various disease symptoms, ranging from fever to life-threatening hemorrhage and even shock. To date, there is still no effective treatment for DENV disease, but only supportive care. DENV nonstructural protein 1 (NS1) has been shown to play a key role in disease pathogenesis. Recent studies have shown that anti-DENV NS1 antibody can provide disease protection by blocking the DENV-induced disruption of endothelial integrity. We previously demonstrated that anti-NS1 monoclonal antibody (mAb) protected mice from all four serotypes of DENV challenge. Here, we generated humanized anti-NS1 mAbs and transferred them to mice after DENV infection. The results showed that DENV-induced prolonged bleeding time and skin hemorrhage were reduced, even several days after DENV challenge. Mechanistic studies showed the ability of humanized anti-NS1 mAbs to inhibit NS1-induced vascular hyperpermeability and to elicit Fcγ-dependent complement-mediated cytolysis as well as antibody-dependent cellular cytotoxicity of cells infected with four serotypes of DENV. These results highlight humanized anti-NS1 mAb as a potential therapeutic agent in DENV infection.

Might Zika virus-associated microcephaly's severity impact deciduous tooth eruption and orofacial structures?

Vaz, F., da Silva Sobrinho, A., Athayde, F., Carvalho, M., Sette-de-Souza, P., Ferreira, S.
29-04-2022
Oral Dis
https://doi.org/10.1111/odi.14227

Objective: to investigate the impact of the severity of microcephaly caused by the Zika virus (MCZ) on tooth eruption and orofacial structures of children. **Design:** This case series study developed the research at the Mens Sana Rehabilitation Center, Arcoverde, Brazil. The study included 27 children diagnosed with MCZ. We performed the data collection in June 2018 through a questionnaire answered by the legal guardians, followed by a clinical examination of the children. The data were analyzed by the Mann-Whitney and Fisher's Exact tests ($p = 0.05$). **Results:** The final sample was composed of 20 children. Of these, 13 (35.0%) had severe microcephaly, 5 (30.0%) had altered sequence of tooth eruption, 10 (50.0%) had delayed eruption, and the mean number of decayed teeth was 2.3. The most identified orofacial changes were teeth grinding habit (65.0%), difficult chewing (50.0%), and non-nutritive sucking (50.0%). Mann-

Whitney test showed that the severity of microcephaly did not affect tooth eruption (p = 0.581). Fisher's exact test showed that the severity of microcephaly was not associated with orofacial changes (p > 0.05). Conclusion: The severity of MCZ does not seem to influence changes in deciduous tooth eruption and the presence of orofacial anomalies.

Impact of temperature on dengue and chikungunya transmission by the mosquito Aedes albopictus.

Mercier, A., Obadia, T., Carraretto, D., Velo, E., Gabiane, G., Bino, S., Vazeille, M., Gasperi, G., Dauga, C., Malacrida, A., Reiter, P., Failloux, A.
28-04-2022
Sci Rep
https://doi.org/10.1038/s41598-022-10977-4

The mosquito Aedes albopictus is an invasive species first detected in Europe in Albania in 1979, and now established in 28 European countries. Temperature is a limiting factor in mosquito activities and in the transmission of associated arboviruses namely chikungunya (CHIKV) and dengue (DENV). Since 2007, local transmissions of CHIKV and DENV have been reported in mainland Europe, mainly in South Europe. Thus, the critical question is how far north transmission could occur. In this context, the Albanian infestation by Ae. albopictus is of interest because the species is present up to 1200 m of altitude; this allows using altitude as a proxy for latitude. Here we show that Ae. albopictus can transmit CHIKV at 28 °C as well as 20 °C, however, the transmission of DENV is only observed at 28 °C. We conclude that if temperature is the key environmental factor limiting transmission, then transmission of CHIKV, but not DENV is feasible in much of Europe.

Zika virus infection triggers the melanization response in Drosophila.

Harsh, S., Tafesh-Edwards, G., Eleftherianos, I.
26-04-2022
Biochim Biophys Acta Mol Basis Dis
https://pubmed.ncbi.nlm.nih.gov/35483592

Dengue Virus and Platelets: From the Biology to the Clinic.

Losada, P., DeLaura, I., Narváez, C.
28-04-2022
Viral Immunol
https://doi.org/10.1089/vim.2021.0135

Dengue is one of the most important vector-borne viral illnesses found in tropical and subtropical regions. Colombia has one of the highest rates of dengue cases in the Americas. Severe dengue virus (DENV) infection presents with capillary leakage, hemorrhage, and organ compromise, eventually leading to death. Over the years, there have been many efforts to develop a vaccine that guarantees protective immunity, but they have been partially successful, as such immunity would need to guarantee protection against four distinct viral serotypes. Absolute platelet count is a laboratory parameter used to monitor the clinical progression of DENV, as infection is often accompanied by thrombocytopenia. Although this finding is well described with respect to the natural history of the disease, there are various hypotheses as to the cause of this rapid decrease, and several *in vivo* and *ex vivo* models have been used to explain the effect of DENV infection on platelets and their precursors. DENV infects and activates platelets, facilitating their elimination through recognition by phagocytic cells and peripheral margination. However, infection also affects the precursors in the bone marrow by modulating megakaryopoiesis. The objective of this article is to explore various proposed mechanisms of DENV-induced thrombocytopenia to better understand the pathophysiology and clinical presentations of this highly relevant viral infection.

Loquacious modulates flaviviral RNA replication in mosquito cells.

Shivaprasad, S., Weng, K., Ooi, Y., Belk, J., Carette, J., Flynn, R., Sarnow, P.
28-04-2022
PLoS Pathog
https://doi.org/10.1371/journal.ppat.1010163

Arthropod-borne viruses infect both mosquito and mammalian hosts. While much is known about virus-host interactions that modulate viral gene expression in their mammalian host, much less is known about the interactions that involve inhibition, subversion or avoidance strategies in the mosquito host. A novel RNA-Protein interaction detection assay was used to detect proteins that directly or indirectly bind to dengue viral genomes in infected mosquito cells. Membrane-associated mosquito proteins Sec61A1 and Loquacious (Loqs) were found to be in complex with the viral RNA. Depletion analysis demonstrated that both Sec61A1 and Loqs have pro-viral functions in the dengue viral infectious cycle. Co-localization and pull-down assays showed that Loqs interacts with viral protein NS3 and both full-length and subgenomic viral RNAs. While Loqs coats the entire positive-stranded viral RNA, it binds selectively to the 3' end of the negative-strand of the viral genome. In-depth analyses showed that the absence of Loqs did not affect translation or turnover of the viral RNA but modulated viral replication. Loqs also displayed pro-viral functions for several flaviviruses in infected mosquito cells, suggesting a conserved role for Loqs in flavivirus-infected mosquito cells.

Generation of Mature DENVs via Genetic Modification and Directed Evolution.

Tse, L., Meganck, R., Dong, S., Adams, L., White, L., Mallory, M., Jadi, R., de Silva, A., Baric, R.
28-04-2022
mBio
https://doi.org/10.1128/mbio.00386-22

Maturation of dengue viruses (DENVs) alters the structure,

immunity, and infectivity of the virion and highly mature particles represent the dominant form *in vivo*. The production of highly mature virions principally relies on the structure and function of the viral premature membrane protein (prM) and its cleavage by the host protease furin. We redeveloped a reliable clonal cell line (VF1) which produces single-round mature DENVs without the need for DENV reverse genetics. More importantly, using protein engineering and directed evolution of the prM cleavage site, we engineered genetically stable mature DENVs in all serotypes independent of cell or host, usually with minimal impact on viral yield. Using these complementary strategies to regulate maturation, we demonstrate that the resulting mature DENVs are antigenically distinct from their isogenic partially mature forms. Given the clinical importance of mature DENVs in immunity, our study provides reliable strategies and reagents for the production of stable, high-titer mature DENVs for DENV antibody neutralization and vaccination immunity studies. Biologically, our data from directed evolution across host species reveals distinct maturation-dependent selective pressures between mammalian and insect cells, verifying the substrate preference between mammalian and insect furin, while hinting at an evolutionary equilibrium of DENV prM cleavage site between its host and vector in nature. IMPORTANCE Mature DENVs represent the dominant form *in vivo* and are the target for vaccine development. Here, we used multiple strategies, including protein engineering and natural and directed evolution to generate DENV1, -2, -3, and -4 variants that are highly mature without compromising replication efficiency compared to the parental strains. Given the clinical importance of mature DENVs in immunity, this work provides a roadmap for engineering highly mature DENV that could apply to future vaccine development. Our directed-evolution data also shed light on the divergent evolutionary relationship of DENVs between its host and vector.

Chikungunya virus seroprevalence in asymptomatic blood donors during an outbreak in the Federal District of Brazil.

da Silva Mendes, A., Cilião-Alves, D., Pimentel, B., Slavov, S., de Araújo, W., Haddad, R.
27-04-2022
Transfus Med
https://doi.org/10.1111/tme.12870

Introduction: Chikungunya virus (CHIKV) is a mosquito-borne alphavirus belonging to the Togaviridae family. The symptomatic infection is characterised by acute febrile disease which generally results in severe arthralgia and myalgia, however, most of the CHIKV infections remain asymptomatic. CHIKV RNA detection in asymptomatic volunteers may be responsible for the transfusion transmission of this infection, especially during outbreaks. There is no information for CHIKV seroprevalence among blood donors from the Federal District of Brazil. Aim: In early 2019, the Federal District of Brazil experienced a CHIKV outbreak, and this study evaluates the anti-CHIKV IgM and IgG presence in a well characterised cohort of blood donors from this region. Methodology: Blood samples were collected from 450 volunteer blood donors during a CHIKV outbreak and tested for the presence of anti-CHIKV IgG and IgM antibodies using ELISA. Results: The CHIKV seroprevalence was 0.89% (n = 4/450) and anti-CHIKV IgM prevalence was 1.11% (n = 5/450). Conclusion: The obtained results demonstrated that at least some of the blood donors have experienced CHIKV infection which can be related to a hypothetical risk of CHIKV transfusion transmission. More studies are necessary in order to examine the impact of CHIKV on blood transfusion.

Bionomic aspects of dengue vectors Aedes aegypti and Aedes albopictus at domestic settings in urban, suburban and rural areas in Gampaha District, Western Province of Sri Lanka.

Dalpadado, R., Amarasinghe, D., Gunathilaka, N., Ariyarathna, N.
27-04-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05261-3

Background: The lack of information on behavioural patterns of Aedes aegypti and Aedes albopictus has become a significant limitation in vector control and disease management programmes. Therefore, the current study was focused on determining some bionomics aspects: breeding, resting, host-seeking and feeding preferences of Ae. aegypti and Ae. albopictus in Sri Lanka. Methods: Larval and adult surveys were conducted from April 2017 to April 2019 monthly in six selected Medical Officer of Health (MOH) areas in Gampaha Distinct, Western province, Sri Lanka, representing urban, suburban and rural settings. Resting preferences of adult mosquitoes were observed from indoor and outdoor places using a Prockopack aspirator. The information on resting height, surface, material and locality was recorded. Human-baited double-net traps were used to determine the host-seeking time of Aedes mosquitoes. Statistical differences in the spatial distribution of mosquitoes in selected MOH areas and prevalence of vectors were analysed using general linear model (GLM). A chi-square test was used to analyse the resting behaviour. Results: Total of 19,835 potential breeding sites were examined at 13,563 premises, and 18.5% (n=1856) were positive for Aedes larvae. Distribution of Ae. aegypti and Ae. albopictus was statistically significant at species level (df=1; F=137.134; P<0.05 GLM) and study setting (df=2; F=8.125; P<0.05). Aedes aegypti breeding was found mainly in temporary removals (18.8%; n=34), discarded non-degradables (12.15%; n=22) and tyres (9.95%; n=18). Natural (14.7%; n=246) and temporary removals (13.6%; n=227) and discarded non-reusable items were the key ovipositing sites for Ae. albopictus. In the adult mosquito survey, the majority was comprised of Ae. albopictus (54.5%; n=999), which denoted exophilic nature (90.8%; n=758), and 45.5% (n=835) represented by Ae. aegypti mosquitoes who were mainly endophilic (84.3%; n=842). Aedes aegypti rested on cloth hangings and curtains, followed by the furniture, while Aedes albopictus was predominant in outdoor vegetation. In both vectors, biting

patterns denoted a typical diurnal pattern with two peaks of host-seeking and biting activity in the morning and afternoon. Conclusions: The majority (80%) of the larval habitats were artificial containers. The use of larvicides for vector control as the prominent measure is questionable since applying these chemicals may target only 20% of the total breeding grounds, which are permanent. The resting places of adult mosquitoes are mainly indoors. Therefore, using thermal space spraying of insecticide may not be appropriate, and indoor residual spraying is recommended as a suitable intervention to target adult mosquitoes. This study warrants a holistic vector control approach for all medically important mosquitoes and insects, ensuring the rational use of finance and resources.

Generation and Characterization of Human-Mouse STING Chimeras That Allow DENV Replication in Mouse Cells.

Zhu, T., Webb, L., Veloz, J., Wilkins, M., Aguirre, S., Fernandez-Sesma, A.
28-04-2022
mSphere
https://doi.org/10.1128/msphere.00914-21

Our group was the first to describe direct antagonism of the cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) pathway by dengue virus (DENV) in human cells, and here, we report new findings on the characterization of the interaction between the DENV nonstructural protein 2B (NS2B)-NS3 (NS2B3) protease complex and STING. We demonstrate interactions between NS2B and the transmembrane domains of human STING and between NS3 and a portion of the cytoplasmic C-terminal domain of human STING. One significant obstacle we face today in the DENV field is the lack of small animal models available that can effectively recapitulate DENV pathogenesis in the early events of infection. The existing mouse models are either immunocompromised mice lacking interferon (IFN) receptors or "humanized" mice reconstituted with human stem cells. However, both approaches fail to capture important aspects of human pathogenesis because they lack critical innate immunity components or have deficiencies in immune cell development or maintenance. As an important step toward developing an immunocompetent mouse model for DENV, we have generated two chimeric human-mouse STING constructs that have promise in retaining both cleavability by NS2B3 and signaling capacity in the mouse. IMPORTANCE This article characterizes the interaction between human STING and DENV viral protease complex NS2B3 by constructing serial deletion mutants of STING. Our findings suggest that DENV nonstructural protein NS2B interacts with the transmembrane domains and NS3 with the C-terminal cyclic dinucleotide binding domain of human STING. Furthermore, as there exists no ideal immunocompetent murine model that can simultaneously support robust DENV replication and recapitulate the clinical manifestation of dengue disease observed in humans, we expressed and characterized two promising human-mouse chimeric STING constructs that can be used for developing a relevant transgenic mouse model to study dengue in the future. Both constructs can activate normal IFN responses in the overexpression system and be cleaved under infection conditions. We believe our findings offer a roadmap to the further development of a murine model that can greatly facilitate antiviral discoveries and vaccine research for DENV.

Development of Azaindole-Based Frameworks as Potential Antiviral Agents and Their Future Perspectives.

Revue de littérature

Urvashi, ., Senthil Kumar, J., Das, P., Tandon, V.
28-04-2022
J Med Chem
https://doi.org/10.1021/acs.jmedchem.2c00444

The azaindole (AI) framework continues to play a significant role in the design of new antiviral agents. Modulating the position and isosteric replacement of the nitrogen atom of AI analogs notably influences the intrinsic physicochemical properties of lead compounds. The intra- and intermolecular interactions of AI derivatives with host receptors or viral proteins can also be fine tuned by carefully placing the nitrogen atom in the heterocyclic core. This wide-ranging perspective article focuses on AIs that have considerable utility in drug discovery programs against RNA viruses. The inhibition of influenza A, human immunodeficiency, respiratory syncytial, neurotropic alpha, dengue, ebola, and hepatitis C viruses by AI analogs is extensively reviewed to assess their plausible future potential in antiviral drug discovery. The binding interaction of AIs with the target protein is examined to derive a structural basis for designing new antiviral agents.

Disrupting the HDAC6-ubiquitin interaction impairs infection by influenza and Zika virus and cellular stress pathways.

Wang, L., Moreira, E., Kempf, G., Miyake, Y., Oliveira Esteves, B., Fahmi, A., Schaefer, J., Dreier, B., Yamauchi, Y., Alves, M., Plückthun, A., Matthias, P.
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Cell Rep
https://pubmed.ncbi.nlm.nih.gov/35476995

The deacetylase HDAC6 has tandem catalytic domains and a zinc finger domain (ZnF) binding ubiquitin (Ub). While the catalytic domain has an antiviral effect, the ZnF facilitates influenza A virus (IAV) infection and cellular stress responses. By recruiting Ub via the ZnF, HDAC6 promotes the formation of aggresomes and stress granules (SGs), dynamic structures associated with pathologies such as neurodegeneration. IAV subverts the aggresome/HDAC6 pathway to facilitate capsid uncoating during early infection. To target this pathway, we generate designed ankyrin repeat proteins (DARPins) binding the ZnF; one of these prevents interaction with Ub in vitro and in cells. Crystallographic analysis shows that it blocks the ZnF pocket where Ub engages. Conditional expression of this

DARPin reversibly impairs infection by IAV and Zika virus; moreover, SGs and aggresomes are downregulated. These results validate the HDAC6 ZnF as an attractive target for drug discovery.

Structure-Based Optimization and Characterization of Macrocyclic Zika Virus NS2B-NS3 Protease Inhibitors.

Huber, S., Braun, N., Schmacke, L., Quek, J., Murra, R., Bender, D., Hildt, E., Luo, D., Heine, A., Steinmetzer, T.
27-04-2022
J Med Chem
https://doi.org/10.1021/acs.jmedchem.1c01860

Zika virus (ZIKV) is a human pathogenic arbovirus. So far, neither a specific treatment nor a vaccination against ZIKV infections has been approved. Starting from our previously described lead structure, a series of 29 new macrocyclic inhibitors of the Zika virus protease containing different linker motifs have been synthesized. By selecting hydrophobic d-amino acids as part of the linker, numerous inhibitors with K_i values < 5 nM were obtained. For 12 inhibitors, crystal structures in complex with the ZIKV protease up to 1.30 Å resolution were determined, which contribute to the understanding of the observed structure-activity relationship (SAR). In immunofluorescence assays, an antiviral effect was observed for compound **26** containing a d-homocyclohexylalanine residue in its linker segment. Due to its excellent selectivity profile and low cytotoxicity, this inhibitor scaffold could be a suitable starting point for the development of peptidic drugs against the Zika virus and related flaviviruses.

Interferon Lambda Signals in Maternal Tissues to Exert Protective and Pathogenic Effects in a Gestational Stage-Dependent Manner.

Casazza, R., Philip, D., Lazear, H.
26-04-2022
mBio
https://doi.org/10.1128/mbio.03857-21

Interferon lambda (IFN-λ) (type III IFN) is constitutively secreted from human placental cells in culture and reduces Zika virus (ZIKV) transplacental transmission in mice. However, the roles of IFN-λ during healthy pregnancy and in restricting congenital infection remain unclear. Here, we used mice lacking the IFN-λ receptor (*Ifnlr1*$^{-/-}$) to generate pregnancies lacking either maternal or fetal IFN-λ responsiveness and found that the antiviral effect of IFN-λ resulted from signaling exclusively in maternal tissues. This protective effect depended on gestational stage, as infection earlier in pregnancy (E7 rather than E9) resulted in enhanced transplacental transmission of ZIKV. In *Ifnar1*$^{-/-}$ dams, which sustain robust ZIKV infection, maternal IFN-λ signaling caused fetal resorption and intrauterine growth restriction. Pregnancy pathology elicited by poly(I·C) treatment also was mediated by maternal IFN-λ signaling, specifically in maternal leukocytes, and also occurred in a gestational stage-dependent manner. These findings identify an unexpected effect of IFN-λ signaling, specifically in maternal (rather than placental or fetal) tissues, which is distinct from the pathogenic effects of IFN-αβ (type I IFN) during pregnancy. These results highlight the complexity of immune signaling at the maternal-fetal interface, where disparate outcomes can result from signaling at different gestational stages. **IMPORTANCE** Pregnancy is an immunologically complex situation, which must balance protecting the fetus from maternal pathogens with preventing maternal immune rejection of non-self fetal and placental tissue. Cytokines, such as interferon lambda (IFN-λ), contribute to antiviral immunity at the maternal-fetal interface. We found in a mouse model of congenital Zika virus infection that IFN-λ can have either a protective antiviral effect or cause immune-mediated pathology, depending on the stage of gestation when IFN-λ signaling occurs. Remarkably, both the protective and pathogenic effects of IFN-λ occurred through signaling exclusively in maternal immune cells rather than in fetal or placental tissues or in other maternal cell types, identifying a new role for IFN-λ at the maternal-fetal interface.

Tetravalent formulation of polymeric nanoparticle-based vaccine induces a potent immune response against dengue virus.

Khan, R., Ahmed, F., Afroz, S., Khan, N.
26-04-2022
Biomater Sci
https://doi.org/10.1039/d2bm00167e

Dengue is a mosquito-borne disease caused by the four serotypes of the dengue virus (DENV 1-4). It is growing at an alarming rate globally, which could be partly attributed to the lack of an effective therapeutic regimen. Therefore, strategies for developing an effective vaccine have gained more significance in the given scenario. Failure of the existing live attenuated vaccine candidates to mount effective and broader protection against all the four serotypes of DENV has generated a new interest in exploring novel strategies for augmenting the efficacy of non-infectious, non-replicating subunit vaccines. In the current study, we employed a new strategy of encapsulating the immunodominant EDIII domain of Envelop protein of all the serotypes of DENV (1-4) into PLGA nanoparticles separately. All four nano formulations were physically mixed to develop a tetravalent nano formulation in combination with TLR agonists. Further, we examined its immunological efficacy using a mouse and *in vitro* infection model system. Interestingly, our results demonstrate that majority of EDIII protein loaded PLGA nanoparticles were polydispersed and less than 1 µm in size with optimal encapsulation efficacy. Tetravalent nanoformulation along with TLR agonists (MPLA + R837) enhanced the magnitude of antigen-specific polyfunctional T cell response. It triggered robust antibody responses in mice concurrent with the increased level of genes involved in the programming of memory B-cell formation and the maintenance and maturation of GCs, leading to the formation of long-lived

plasma cells secreting antigen-specific antibodies. Further assessment revealed that tetravalent nanoformulation in combination with TLR ligands upon immunization in mice aids in the enhanced production of serotype-specific neutralizing antibodies, which can effectively neutralize all the four serotypes of DENV (DENV 1-4). The findings of this study reveal a new strategy for enhancing the immunogenicity of vaccine candidates and might pave the way for the development of a tetravalent vaccine against all the serotypes of Dengue Virus.

Myracrodruon urundeuva leaf lectin damages exochorionic cells and binds to the serosal cuticle of *Aedes aegypti* eggs.

Alves, R., Prazeres, G., da Silva, A., da Silva, A., Nascimento, J., Sá, R., Gonçalves, G., Brayner, F., Alves, L., do Amaral Ferraz Navarro, D., Filho, P., Fontes, A., Napoleão, T., Paiva, P.

09-04-2022

3 Biotech

https://doi.org/10.1007/s13205-022-03172-9

In recent years, lectins have been identified as alternative agents against *Aedes aegypti* during the aquatic phases of its life cycle. For example, chitin-binding lectin from *Myracrodruon urundeuva* leaf (MuLL) can function as a larvicide. In this study, we investigated whether MuLL can also act as an ovicide against this insect. *Aedes aegypti* eggs were incubated with MuLL for 72 h to determine the concentration at which the hatching rate reduces by 50% (EC_{50}). The effects of MuLL on the egg surface structure were evaluated using scanning electron microscopy (SEM), and the possible interaction of MuLL with the internal structures of eggs and embryos was investigated using MuLL-fluorescein isothiocyanate (FITC) conjugate. MuLL acted as an ovicidal agent with an EC_{50} of 0.88 mg/mL. The SEM analysis revealed that eggs treated with MuLL for 24 and 48 h no longer had tubercles and did not show a well-defined exochorionic network. In addition, deformation and degeneration of the surface were observed after 72 h. Fluorescence microscopy showed that MuLL penetrated the eggs 48 h after incubation and was detected in the upper portion of the embryo's gut. After 72 h, MuLL was observed in the serosal cuticle and digestive tract. In conclusion, MuLL can function as an ovicidal agent against *A. aegypti* through damage to the surface and internal structures of the eggs.

Domestic Dogs as Sentinels for West Nile Virus but not Aedes-borne Flaviviruses, Mexico.

Davila, E., Fernández-Santos, N., Estrada-Franco, J., Wei, L., Aguilar-Durán, J., López-López, M., Solís-Hernández, R., García-Miranda, R., Velázquez-Ramírez, D., Torres-Romero, J., Chávez, S., Cruz-Cadena, R., Navarro-López, R., de León, A., Guichard-Romero, C., Martin, E., Tang, W., Frank, M., Borucki, M., Turell, M., Pauvolid-Corrêa, A., Rodríguez-Pérez, M., Ochoa-Díaz-López, H., Hamer, S., Hamer, G.

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Emerg Infect Dis

https://doi.org/10.3201/eid2805.211879

We tested 294 domestic pet dogs in Mexico for neutralizing antibodies for mosquito-borne flaviviruses. We found high (42.6%) exposure to West Nile virus in Reynosa (northern Mexico) and low (1.2%) exposure in Tuxtla Gutierrez (southern Mexico) but very limited exposure to Aedes-borne flaviviruses. Domestic dogs may be useful sentinels for West Nile virus.

An algorithmic approach to identifying the aetiology of acute encephalitis syndrome in India: results of a 4-year enhanced surveillance study.

Ravi, V., Hameed, S., Desai, A., Mani, R., Reddy, V., Velayudhan, A., Yadav, R., Jain, A., Saikia, L., Borthakur, A., Sharma, A., Mohan, D., Bhandopadhyay, B., Bhattacharya, N., Inamdar, L., Hossain, S., Daves, S., Sejvar, J., Dhariwal, A., Sen, P., Venkatesh, S., Prasad, J., Laserson, K., Srikantiah, P.

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Lancet Glob Health

https://pubmed.ncbi.nlm.nih.gov/35427525

Background: Annual outbreaks of acute encephalitis syndrome pose a major health burden in India. Although Japanese encephalitis virus (JEV) accounts for around 15% of reported cases, the aetiology of most cases remains unknown. We aimed to establish an enhanced surveillance network and to use a standardised diagnostic algorithm to conduct a systematic evaluation of acute encephalitis syndrome in India. Methods: In this large-scale, systematic surveillance study in India, patients presenting with acute encephalitis syndrome (ie, acute onset of fever with altered mental status, seizure, or both) to any of the 18 participating hospitals across Uttar Pradesh, West Bengal, and Assam were evaluated for JEV (serum and cerebrospinal fluid [CSF] IgM ELISA) per standard of care. In enhanced surveillance, JEV IgM-negative specimens were additionally evaluated for scrub typhus, dengue virus, and West Nile virus by serum IgM ELISA, and for Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, dengue virus, herpes simplex virus, and enterovirus by CSF PCR across five referral laboratories. In 2017, chikungunya and Leptospira serum IgM by ELISA and Zika virus serum and CSF by PCR were also tested. Findings: Of 10 107 patients with acute encephalitis syndrome enrolled in enhanced surveillance between Jan 1, 2014, and Dec 31, 2017, 5734 (57·8%) of 9917 participants with available data were male and 6179 (62·7%) of 9856 were children aged 15 years and younger. Among patients who provided a sample of either CSF or serum in enhanced surveillance, an aetiology was identified in 1921 (33·2%) of 5786 patients enrolled between 2014 and 2016 and in 1484 (34·3%) of 4321 patients enrolled in 2017. The most commonly identified aetiologies were JEV (1023 [17·7%] of 5786 patients), scrub typhus (645 [18·5%] of 3489), and dengue virus (161 [5·2%] of 3124). Among participants who provided both CSF and serum specimens, an aetiology was identified in 1446 (38·3%) of 3774 patients enrolled between 2014 and 2016 and in 936 (40·3%) of 2324 enrolled in 2017, representing a 3·1-times increase in the number of patients with acute encephalitis syndrome with an identified

aetiology compared with standard care alone (299 [12·9%]; p<0·0001). **Interpretation:** Implementation of a systematic diagnostic algorithm in an enhanced surveillance platform resulted in a 3·1-times increase in identification of the aetiology of acute encephalitis syndrome, besides JEV alone, and highlighted the importance of scrub typhus and dengue virus as important infectious aetiologies in India. These findings have prompted revision of the national testing guidelines for this syndrome across India. **Funding:** US Centers for Disease Control and Prevention.

Anti-viral activity of thiazole derivatives: an updated patent review.

Farghaly, T., Alsaedi, A., Alenazi, N., Harras, M.
27-04-2022
Expert Opin Ther Pat
https://doi.org/10.1080/13543776.2022.2067477

Introduction: Several viral infections cause life-threatening consequences in humans, making them the most serious public health concerns. Despite the fact that several antiviral medicines are available on the market, there is no full treatment for many important viral infections. To date, antiviral medicines have significantly reduced the spread of epidemics, but their continued use has resulted in the creation of drug-resistant variants throughout time. As a result, the development of new, safe, and efficient antiviral drugs is critical. **Areas covered:** This review covered reports in the patent literature in the period 2014 to the first quarter of 2021 on the antiviral activities of thiazole derivatives. These molecules were reported to inhibit a wide range of viruses including influenza viruses, coronaviruses, herpes viruses, hepatitis B and C, bovine viral diarrhea virus, chikungunya virus and human immunodeficiency viruses. **Expert opinion:** The most bioactive molecules can be used as lead structures for the development of new thiazole compounds with potent and selective antiviral activity. In addition, more efforts are needed to better understand the host-virus interactions for the discovery and development of new therapeutic agents and creative treatment strategies that are supposed to improve rates of clinical cure of the serious viruses.

Septin 2 interacts with dengue virus replication complex proteins and participates in virus replication in mosquito cells.

Rubio-Miranda, J., Cázares-Raga, F., Coy-Arechavaleta, A., Viettri, M., Cortes-Martínez, L., Lagunes-Guillén, A., Chávez-Munguía, B., Ludert, J., Hernández-Hernández, F.
27-03-2022
Virology
https://pubmed.ncbi.nlm.nih.gov/35390695

Septins are a family of GTP-binding proteins identified in insects and mammals. Septins are components of the cytoskeleton and participate in cytokinesis, chromosomal segregation, intracellular vesicular traffic, and response to pathogens. Human septin 6 was identified as necessary for hepatitis C virus replication. Information about host factors necessary for flavivirus replication in mosquitoes is scarce. Thus, the role of septins in the replicative cycle of dengue virus in Aedes spp. derived cells was investigated. Through bioinformatic analysis, sequences of septin-like proteins were identified. Infected mosquito cells showed increased expression of Sep2. Colocalization analysis, proximity ligation and immunoprecipitation assays indicated that Sep2 interacts with proteins E, NS3 and NS5, but not NS1. Immunoelectron microscopy evidenced the presence of AalSep2 in replicative complexes. Finally, silencing of Sep2 expression resulted in a significant decrease in virus progeny, indicating that Sep2 is a host factor participating in dengue virus replication in mosquito cells.

A Flexible Statistical Framework for Estimating Excess Mortality.

Acosta, R., Irizarry, R.
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Epidemiology
https://doi.org/10.1097/EDE.0000000000001445

Quantifying the impact of natural disasters or epidemics is critical for guiding policy decisions and interventions. When the effects of an event are long-lasting and difficult to detect in the short term, the accumulated effects can be devastating. Mortality is one of the most reliably measured health outcomes, partly due to its unambiguous definition. As a result, excess mortality estimates are an increasingly effective approach for quantifying the effect of an event. However, the fact that indirect effects are often characterized by small, but enduring, increases in mortality rates present a statistical challenge. This is compounded by sources of variability introduced by demographic changes, secular trends, seasonal and day of the week effects, and natural variation. Here, we present a model that accounts for these sources of variability and characterizes concerning increases in mortality rates with smooth functions of time that provide statistical power. The model permits discontinuities in the smooth functions to model sudden increases due to direct effects. We implement a flexible estimation approach that permits both surveillance of concerning increases in mortality rates and careful characterization of the effect of a past event. We demonstrate our tools' utility by estimating excess mortality after hurricanes in the United States and Puerto Rico. We use Hurricane Maria as a case study to show appealing properties that are unique to our method compared with current approaches. Finally, we show the flexibility of our approach by detecting and quantifying the 2014 Chikungunya outbreak in Puerto Rico and the COVID-19 pandemic in the United States. We make our tools available through the excessmort R package available from https://cran.r-project.org/web/packages/excessmort/.

ZIKV B-cell epitopes for immunodiagnostic tests.

Kubiszeski, J., da Silva, D., Menezes, G., da Silva, R., Zini, N., Nogueira, M., Pena, L., Piccoli, J., Cilli, E., da Silva, J., Bronzoni,

R.
11-03-2022
J Immunol Methods
https://pubmed.ncbi.nlm.nih.gov/35288195

The use of serological tests is valuable to diagnose Zika virus (ZIKV) infection and carry out epidemiological surveillance. However, ZIKV serological tests may result in false positives due to cross-reactivity between antibodies against other Flavivirus, especially dengue virus that worldwide disseminated. We used three online tools to predict amino acid sequences of B-cell epitopes. We selected and synthetized two epitopes that showed appropriate features in the molecular dynamic simulation and demonstrated to be suitable for serological assays.

A Retrospective Overview of Zika Virus Evolution in the Midwest of Brazil.

Giovanetti, M., Pereira, L., Adelino, T., Fonseca, V., Xavier, J., de Araújo Fabri, A., Slavov, S., da Silva Lemos, P., de Almeida Marques, W., Kashima, S., Lourenço, J., de Oliveira, T., Campelo de Albuquerque, C., Freitas, C., Peterka, C., da Cunha, R., Mendonça, A., Lemes da Silva, V., Alcantara, L.
07-03-2022
Microbiol Spectr
https://doi.org/10.1128/spectrum.00155-22

Since the introduction of the Zika virus (ZIKV) into Brazil in 2015, its transmission dynamics have been intensively studied in many parts of the country, although much is still unknown about its circulation in the midwestern states. Here, using nanopore technology, we obtained 23 novel partial and near-complete ZIKV genomes from the state of Goiás, located in the Midwest of Brazil. Genomic, phylogenetic, and epidemiological approaches were used to retrospectively explore the spatiotemporal evolution of the ZIKV-Asian genotype in this region. As a likely consequence of a gradual accumulation of herd immunity, epidemiological data revealed a decline in the number of reported cases over 2018 to 2021. Phylogenetic reconstructions revealed that multiple independent introductions of the Asian lineage have occurred in Goiás over time and revealed a complex transmission dynamic between epidemic seasons. Together, our results highlight the utility of genomic, epidemiological, and evolutionary methods to understand mosquito-borne epidemics. IMPORTANCE Despite the considerable morbidity and mortality of arboviral infections in Brazil, such as Zika, chikungunya, dengue fever, and yellow fever, our understanding of these outbreaks is hampered by the limited availability of genomic data to track and control the epidemic. In this study, we provide a retrospective reconstruction of the Zika virus transmission dynamics in the state of Goiás by analyzing genomic data from areas in Midwest Brazil not covered by other previous studies. Our study provides an understanding of how ZIKV initiates transmission in this region and reveals a complex transmission dynamic between epidemic seasons. Together, our results highlight the utility of genomic, epidemiological, and evolutionary methods to understand mosquito-borne epidemics, revealing how this toolkit can be used to help policymakers prioritize areas to be targeted, especially in the context of finite public health resources.

Interleukin-17 Contributes to Chikungunya Virus-Induced Disease.

Liu, X., Poo, Y., Alves, J., Almeida, R., Mostafavi, H., Tang, P., Bucala, R., Teixeira, M., Taylor, A., Zaid, A., Mahalingam, S.
07-03-2022
mBio
https://doi.org/10.1128/mbio.00289-22

Alphaviral arthritides caused by mosquito-borne arboviruses such as chikungunya virus (CHIKV) can persist for months after the initial acute disease. Here, we investigated the contribution of interleukin-17 (IL-17), a cytokine involved in chronic autoimmune arthropathies such as rheumatoid arthritis, to the development of alphaviral arthropathy. Sera from CHIKV-infected patients who displayed both acute and chronic disease showed high levels of IL-17, IL-6, IL-21, IL-22, and IL-23, especially during the chronic phase of disease. We sought to validate these findings using a mouse model of CHIKV infection and disease using wild-type and IL-17A-deficient mice. Mice were infected with CHIKV, and joint and muscle tissues were harvested at designated time points. Tissue infiltrates were examined by immunohistochemistry, and tissue mRNA and protein expression of cytokines was assessed. Joint and muscle pathology was assessed using histology. CHIKV-infected mice lacking IL-17A showed reduced tissue inflammation and neutrophil infiltration, compared to wild-type mice. These investigations showed a role for IL-17 in the acute phase of CHIKV infection and also during the postacute disease resolution phase. IMPORTANCE CHIKV has been prevalent in Africa, Asia, and the Indian Ocean Islands for decades. There are currently no clinically approved vaccines or specific antiviral drugs targeting CHIKV. The upregulation of IL-17 detected in CHIKV disease patients and the reduced disease seen in IL-17-deficient mice suggest a correlation between IL-17 signaling pathways and CHIKV-induced arthritic inflammation. With an established role in contributing to the pathogenesis of immune-mediated diseases, such as psoriatic arthritis and rheumatoid arthritis, IL-17 signaling plays an important role in alphavirus arthritides.

A multicenter cohort study of severe dengue and critically ill influenza patients with elevated cardiac troponin-I: Difference clinical features and high mortality.

Lee, I., Chen, Y., Huang, C., Hsu, J., Chang, Y., Kuo, H., Tai, C., Lee, N.
26-02-2022
Travel Med Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35231642

Background: As cardiac involvement can cause serious complications and death, understanding its role in acute dengue and influenza virus infections is important. Methods:

We provide a comparative evaluation of severe dengue and critically ill influenza patients with elevated cardiac troponin-I (cTnI) from 2014 to 2019. Inclusion criteria included patients in which cTnI test were ordered. Patient without cTnI test was excluded. **Results:** During the study period, 82 (41 severe dengue and 41 critically ill influenza) patients had cTnI elevations, and 81 (35 severe dengue and 46 critically ill influenza) patients had a single normal cTnI test. Severe dengue patients with cTnI elevations had a significantly higher incidences of acute kidney injury, gastrointestinal bleeding, early mortality (≤7 after illness onset) and in-hospital mortality than those with severe dengue and single normal cTnI test. Significantly higher aspartate aminotransferase (AST) levels and higher incidence of gastrointestinal bleeding was observed in critically ill influenza patients with cTnI elevations compared to critically ill influenza patients with single normal cTnI measurement. Of the patients with cTnI elevations, the early and in-hospital mortality rates were 53.6% and 65.8%, respectively, in severe dengue patients, and 7.3% and 46.3%, respectively, in critically ill influenza patients. Significantly higher early mortality rates were observed in severe dengue patients with elevated cTnI levels than in critically ill influenza patients with cTnI elevations. Critically ill influenza patients with elevated cTnI levels had significantly higher incidences of pneumonia, pneumothorax, and bacteremia than severe dengue patients with cTnI elevations. Multivariate analysis revealed elevated AST (>1000U/L) (95% confidence interval [CI]: 1.690-143.174) was an independent risk factor for in-hospital mortality in severe dengue patients with elevated cTnI levels. Leukocytosis (95% CI: 1.079-1.124) and thrombocytopenia (95% CI: 2.739-5.821) were independently correlated with in-hospital mortality in critically ill influenza patients with cTnI elevations. **Conclusions:** Differences in clinical features between severe dengue and critically ill influenza patients with cTnI elevations. High early mortality rate was observed in severe dengue patients with cardiac involvement. In contrast, most critically ill influenza patients died ≥2 weeks after the onset of illness, regardless of cTnI elevations. Our report has important clinical implications for the timely recognition and management of cardiac complication in patients with acute dengue and influenza virus infections.

Lifetime pathogen burden, inflammatory markers, and depression in community-dwelling older adults.

Lu, Y., Liu, B., Tan, C., Pan, F., Larbi, A., Ng, T.
22-02-2022
Brain Behav Immun
https://pubmed.ncbi.nlm.nih.gov/35202734

The link between pathogen exposure and mental health has long been hypothesized, but evidence remains limited. We investigated the association of seropositivity to common pathogens and total pathogen burden with depression and mental health and explored the role of mediating inflammatory cytokines. We profiled in 884 participants in the Singapore Longitudinal Ageing Studies, mean (SD) age: 67.9 (8.1) years, their seropositivities for 11 pathogens (CMV, HSV 1, HSV 2, HHV-6, EBV, VZV, RSV, Dengue, Chikungunya, H. Pylori and Plasmodium) and pathogen burden, Geriatric Depression Scale (GDS) score at baseline and 3-4 and 6-8 years follow-up, and baseline Mental Component Score (MCS) of 12-Item Short Form Survey (SF-12). Inflammatory markers included CRP, TNF-α, IL-6, MIP-1α, sgp130, sTNF-RI, sTNF-RII, C3a, and MCP-2. Controlling for age, sex, ethnicity, education, marital status, living alone, and smoking status, high pathogen burden (7 + cumulative infections) compared to low pathogen burden (1-5 cumulative infections) was significantly associated with period prevalence (the highest GDS score from baseline and follow-up measurements) of depressive symptoms (OR = 2.36, 95% CI = 1.05-5.33) and impaired mental health (OR = 2.25, 95% CI = 1.18-4.30). CMV seropositivity and HSV1 seropositivity, which are highly prevalent and most widely studied, were associated with estimated 2-fold increased odds of depression, but only HSV1 seropositivity was significantly associated with depression after adjusting for confounders. Notably, adjusted for confounders, RSV, H. pylori and Plasmodium seropositivity were significantly associated with increased odds, and Dengue seropositivity was associated with unexpectedly deceased odds of depressive symptoms and impaired mental health. The association of pathogen exposure with depression and mental health were at least in parts explained by inflammatory markers. Adding certain inflammatory markers to the models attenuated or weakened the association. Bootstrap method showed that MIP-1α significantly mediated the association between pathogen burden and mental health. In conclusion, lifelong pathogen burden and specific infections are associated with depression and impaired mental health in older adults.

ARBO: Arbovirus modeling and uncertainty quantification toolbox.

Tosin, M., Dantas, E., Cunha, A., Morrison, R.
16-02-2022
Softw Impacts
https://doi.org/10.1016/j.simpa.2022.100252

The ongoing pandemic of COVID-19 has highlighted the importance of mathematical tools to understand and predict outbreaks of severe infectious diseases, including arboviruses such as Zika. To this end, we introduce ARBO, a package for simulation and analysis of arbovirus nonlinear dynamics. The implementation follows a minimalist style, and is intuitive and extensible to many settings of vector-borne disease outbreaks. This paper outlines the main tools that compose ARBO, discusses how recent research works about the Brazilian Zika outbreak have explored the package's capabilities, and describes its potential impact for future works on mathematical epidemiology.

Envelope E protein of dengue virus and phospholipid binding to the late endosomal membrane.

Villalaín, J.
12-02-2022
Biochim Biophys Acta Biomembr
https://pubmed.ncbi.nlm.nih.gov/35167815

Flaviviruses include many significant human pathogens, comprising dengue, West Nile, Yellow fever, Japanese encephalitis, Zika and tick-borne encephalitis viruses and many others, affecting millions of people in the world. These viruses have produced important epidemics in the past, they continue to do it and they will undoubtedly continue to do so in the future. Flaviviruses enter into the cells via receptor-mediated endocytosis by fusing its membrane with the endosomal membrane in a pH-dependent manner with the help of the envelope E protein, a prototypical class II membrane fusion protein. The envelope E protein has a conserved fusion peptide at its distal end, which is responsible in the first instance of inserting the protein into the host membrane. Since the participation of other segments of the E protein in the fusion process should not be ruled out, we have used atomistic molecular dynamics to study the binding of the distal end of domain II of the envelope E protein from Dengue virus (DENV) with a complex membrane similar to the late-endosome one. Our work shows that not only the fusion peptide participates directly in the fusion, but also two other sequences of the protein, next to the fusion peptide it in the three-dimensional structure, are jointly wrapped in the fusion process. Overall, these three sequences represent a new target that would make it possible to obtain effective antivirals against DENV in particular and Flaviviruses in general.

Characterization of Guillain-Barré Syndrome in the integrated development region of the Federal District and Surrounding Areas (RIDE), Brazil, between 2017 and 2019.

Oliveira, A., Silva, A., Manga Aridjae, U., Bastos, M., Wachira, V., Gallo, L.
10-02-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35150642

Introduction: Guillain-Barré Syndrome (GBS) is an acute immune-mediated polyneuropathy that primarily affects the peripheral nerves. Following the Zika virus outbreak in Latin America, all the Latin American and Brazilian studies conducted reported an increase in the incidence of GBS. The present study aims to characterize the clinical and demographic profile of patients with GBS, according to electrophysiological estudies. Methods: This is a clinical cohort study based on data from medical charts and interviews conducted at the homes of GBS cases identified by three data sources, admitted to and treated at a tertiary referral hospital between March 2017 and May 2019. Results: There was a high level of diagnostic certainty among the 51 GBS cases monitored, with most classified as exhibiting acute inflammatory demyelinating polyneuropathy (AIDP). The majority of the individuals were of working age, with an average schooling level. Diarrhea and upper respiratory tract infection were the previous events most reported. Most cases were admitted to the hospital unable to walk and the main complication identified was aspiration pneumonia. Conclusion: The findings indicate the need to rethink the care of patients with GBS in order to minimize the possibility of future complications during hospitalization that may lead to unfavorable outcomes.

Neglected tropical rheumatic diseases.

Revue de littérature

Sahoo, R., Wakhlu, A., Agarwal, V.
10-02-2022
Clin Rheumatol
https://doi.org/10.1007/s10067-022-06090-6

The complexities of dealing with rheumatic diseases in tropical countries are diverse and likely due to limited health care infrastructure, lack of diagnostic and therapeutic facilities, impact of dominant prevailing diseases, and the challenges of differentiating from infectious and non-infectious disease mimics. Several tropical diseases present with musculoskeletal and rheumatic manifestations and often pose a diagnostic dilemma to rheumatologists. The diagnosis is often delayed or the disease is misdiagnosed, leading to poor patient outcomes. Endemic tropical diseases like tuberculosis and leprosy have myriad rheumatic presentations and remain important differentials to consider in patients with rheumatic manifestations. Infection with human immunodeficiency virus is a great masquerade and can mimic manifestations of multiple diseases. The role of viral infections in triggering and perpetuating autoimmunity is well known and chikungunya arthritis is a classic example of the same. This review highlights the rheumatic manifestations of tropical diseases and aims to create awareness among the caregivers. Key Points • It is crucial to be aware and identify infectious diseases presenting with rheumatic manifestations in the tropics. • Presentations akin to classic rheumatic syndromes such as rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus and vasculitis are common.

Water quality characteristics of breeding habitats in relation to the density of Aedes aegypti and Aedes albopictus in domestic settings in Gampaha district of Sri Lanka.

Dalpadado, R., Amarasinghe, D., Gunathilaka, N.
31-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35114170

In spite of the unavailability of measures to target dengue control in human populations, the promising way of combating the disease is by controlling vector mosquito larvae and their breeding habitats. Water quality characteristics of the breeding habitats of dengue vectors are among the crucial parameters that determine the female mosquito's oviposition and breeding. Therefore, a cross-sectional study was conducted to investigate the habitat characteristics of dengue

vector mosquitoes by assessing the water quality of positive breeding habitats using the weighted arithmetic water quality index (WQI). The present study was conducted in domestic areas of the selected medical officer of health areas of the Gampaha district, Sri Lanka, from 2017 to 2019. Water quality characteristics of breeding habituations were measured and analyzed. The relationship between water quality parameters in breeding habitats with the occurrence of mosquito species was assessed using Kruskal-Wallis one-way analysis of variance, followed by pairwise comparison using Dunn's test and Mann-Whitney U test at a 5% level of significance. This study revealed that the temperature of Aedes mosquito breeding water ranged between 25.3 and 39.8 °C, and bred at temperatures as high as 39.8 °C in discarded receptacles. The results indicated that Ae. aegypti was prominent in alkaline water ranging between 7.5 and 8.5 pH, whereas Ae. albopictus was abundant in water with a pH range of 6.5-7.5. Both species of Aedes inhabited waters of low turbidity and TDS level. Ae. aegypti and Ae. albopictus immatures were prominent in water where TDS levels ranged between 250 and 350 ppm. The mean conductivity in the mosquito breeding water was recorded as 228.3 ± 63.9 µs/cm. The study revealed that Aedes mosquitoes could breed in water with a mean dissolved oxygen level of 6.9 ± 0.7 mg/L, ranging between 6.35 ± 1.09 mg/L and 7.28 ± 0.26 mg/L. The water quality indices were calculated for the eight previously identified breeding habitat categories of Aedes mosquitoes.

Viral fever of unknown origin during COVID-19 and dengue outbreaks in Pakistan: Is media spreading panic during pandemic?

Khan, Y., Salman, M., Butt, M., Mallhi, T.
18-01-2022
J Med Virol
https://doi.org/10.1002/jmv.27569

High-resolution intracranial vessel wall imaging in cerebral viral infections evaluations.

Vyas, S., Choudhary, N., Modi, M., Sankhyan, N., Suthar, R., Saini, A., Bansal, A., Sharma, N., Singh, P.
16-10-2021
Neuroradiology
https://doi.org/10.1007/s00234-021-02831-7

Purpose: Vascular complications can be seen in various viral CNS infections. Variable neuro-imaging findings have been described in the literature elucidating the parenchymal changes with vascular involvement. Vessel wall imaging (VWI) can help to detect these vascular involvements. We aimed to describe the role and usefulness of VWI in the evaluation of various viral CNS infections. Methods: In this prospective study, we included 15 cases of various diagnosed viral CNS infections (varicella, HIV encephalopathy, HSV encephalitis, Japanese encephalitis, dengue, COVID-19). VWI and time-of-flight MR angiography (TOF MRA) were included in imaging protocol. All cases were evaluated for the presence of cerebral parenchymal changes, vascular enhancement, and vascular stenosis. Results: We found infarctions in all 5 cases of varicella, 1 case of HIV encephalopathy, and 1 case of COVID-19 encephalopathy. All these cases also showed vascular enhancement and stenosis on VWI. The rest of the cases, including 1 case of HIV encephalopathy, 3 cases of herpes encephalitis, 2 cases of dengue, and 2 cases of Japanese encephalitis did not have any vascular complication, and also did not show vascular enhancement or stenosis. Conclusion: VWI can be useful in the detection of vascular involvement in various viral infections of CNS which show a relatively higher cerebrovascular complication rate like varicella, HIV encephalopathy, and COVID-19. However, VWI may not be useful in the routine evaluation of other viral infections like herpes, dengue, and Japanese encephalitis, which have a very low rate of cerebrovascular complication rate.

Assessing Interventions That Prevent Multiple Infectious Diseases: Simple Methods for Multidisease Modeling.

Claypool, A., Goldhaber-Fiebert, J., Brandeau, M.
11-08-2021
Med Decis Making
https://doi.org/10.1177/0272989X211033287

Background: Many cost-effectiveness analyses (CEAs) only consider outcomes for a single disease when comparing interventions that prevent or treat 1 disease (e.g., vaccination) to interventions that prevent or treat multiple diseases (e.g., vector control to prevent mosquito-borne diseases). An intervention targeted to a single disease may be preferred to a broader intervention in a single-disease model, but this conclusion might change if outcomes from the additional diseases were included. However, multidisease models are often complex and difficult to construct. Methods: We present conditions for when multiple diseases should be considered in such a CEA. We propose methods for estimating health outcomes and costs associated with control of additional diseases using parallel single-disease models. Parallel modeling can incorporate competing mortality and coinfection from multiple diseases while maintaining model simplicity. We illustrate our approach with a CEA that compares a dengue vaccine, a chikungunya vaccine, and mosquito control via insecticide and mosquito nets, which can prevent dengue, chikungunya, Zika, and yellow fever. Results: The parallel models and the multidisease model generated similar estimates of disease incidence and deaths with much less complexity. When using this method in our case study, considering only chikungunya and dengue, the preferred strategy was insecticide. A broader strategy-insecticide plus long-lasting insecticide-treated nets-was not preferred when Zika and yellow fever were included, suggesting the conclusion is robust even without the explicit inclusion of all affected diseases. Limitations: Parallel modeling assumes independent probabilities of infection for each disease. Conclusions: When multidisease effects are important, our parallel modeling method can be used to model multiple diseases accurately while avoiding additional complexity.

Orofacial features in children with microcephaly associated with Zika virus: A scoping review.

Revue de littérature

da Silva Sobrinho, A., Ramos, L., Maciel, Y., Maurício, H., Cartaxo, R., Ferreira, S., Sette-de-Souza, P.
28-02-2021
Oral Dis
https://doi.org/10.1111/odi.13804

Objective: To analyze published scientific evidence about the most common orofacial disorders in children with microcephaly associated with ZIKV infection. **Methods:** Through a scoping review, we respond to the search question was formulated: "What are the orofacial alterations in children with microcephaly associated with ZIKV?" It was performed a search in PubMed, EMBASE, Scopus, and Health Virtual Library. It was selected papers wrote in English, Portuguese, or Spanish. An evidence quality analysis was performed using the Agency for Healthcare Research and Quality classification. **Results:** It was included 11 studies performed in the Brazilian Northeast region. The studies were carried out between 2018 and 2020. The main related alterations were delay in the tooth-eruption and deformation in the oral structures. **Conclusion:** The results observed in our work show moderate scientific evidence regarding the association of ZIKV with orofacial alterations in children with microcephaly due to the classifications of the quality of evidence of each one of the included studies. The main changes reported were in the chronology of tooth eruption, alteration in teeth, and oral structures.

How Americans Make Sense of Two Novel Pandemics.

Fink, E., Smith, R., Cai, D., Jung, H., Woelfel, J.
04-01-2021
Health Commun
https://doi.org/10.1080/10410236.2020.1857506

Using Galileo theory and method of multidimensional scaling (MDS), we compared the psychological distances between concepts related to two pandemic viruses, Zika and COVID-19. Surveys (Zika, $N = 410$; COVID-19, $N = 291$) were used to investigate the role of media use and interpersonal communication on the relationship between 10 concepts in multidimensional spaces. We asked these four research questions: Do the two spaces represent the two pandemics similarly? What is the relationship of *me* and of *people* to each pandemic? What is the effect of virus-related media use and interpersonal talk on the pandemic space? What are optimal messages for moving *me* closer to *Zika* and to *COVID-19*? Media use influenced the distances for both pandemics: With greater media use, the concepts were closer in the Zika space and further apart in the COVID-19 space. Interpersonal communication was associated with few differences in the spaces. Based on the psychological distances between concepts, optimal messages were identified: For Zika, a message with two concepts, *people* and *women*, is predicted to be most effective to move *Zika* to the concept *me*, whereas for COVID-19, a message with *people* is predicted to be most effective to move *COVID-19* to *me*.

Druggability assessment of precursor membrane protein as a target for inhibiting the Zika virus.

Mulgaonkar, N., Wang, H., King, M., Fernando, S.
01-12-2020
J Biomol Struct Dyn
https://doi.org/10.1080/07391102.2020.1851304

The Zika virus (ZIKV), a significant zoonotic flavivirus, was neglected as a human pathogen until the recent epidemic. The rapid geographic spread of the virus and association with neurological disorders has created a global public health concern pressing the need for anti-ZIKV drugs. Previous ZIKV drug discovery research has focused on three primary targets, RNA-dependent RNA polymerase, envelope protein, and viral proteases, and none has yet resulted in a commercially viable inhibitor. In the quest for finding effective inhibitors, it is important to expand the number of targets available for drug discovery research. To this end, the ZIKV precursor membrane protein (prM) comes to the forefront as a potential target due to its critical role in virus infectivity and pathogenicity. prM acts as a chaperone for envelope protein folding and prevents premature fusion of virions to the host membrane and has not been attempted as a drug target before. One critical requirement for a protein to be an effective target is the ability of the protein to be druggable, i.e. having active sites that can bind to specific ligands. In this work, the druggability of prM was assessed via molecular docking combined molecular dynamics simulations followed binding affinity kinetics studies. Compounds that had a high affinity to the prM protein were screened *in silico* and ligand-binding free energies were computed using molecular mechanics with generalized Born and surface area continuum solvation (MM-GBSA) method. *In vitro* binding kinetics via biolayer interferometry (BLI) and interaction analysis confirmed that prM could be targeted for drug discovery to combat ZIKV infection.Communicated by Ramaswamy H. Sarma.

RAGE

Making genomic surveillance deliver: A lineage classification and nomenclature system to inform rabies elimination.

Campbell, K., Gifford, R., Singer, J., Hill, V., O'Toole, A., Rambaut, A., Hampson, K., Brunker, K.
02-05-2022
PLoS Pathog
https://doi.org/10.1371/journal.ppat.1010023

The availability of pathogen sequence data and use of genomic surveillance is rapidly increasing. Genomic tools and classification systems need updating to reflect this. Here,

rabies virus is used as an example to showcase the potential value of updated genomic tools to enhance surveillance to better understand epidemiological dynamics and improve disease control. Previous studies have described the evolutionary history of rabies virus, however the resulting taxonomy lacks the definition necessary to identify incursions, lineage turnover and transmission routes at high resolution. Here we propose a lineage classification system based on the dynamic nomenclature used for SARS-CoV-2, defining a lineage by phylogenetic methods for tracking virus spread and comparing sequences across geographic areas. We demonstrate this system through application to the globally distributed Cosmopolitan clade of rabies virus, defining 96 total lineages within the clade, beyond the 22 previously reported. We further show how integration of this tool with a new rabies virus sequence data resource (RABV-GLUE) enables rapid application, for example, highlighting lineage dynamics relevant to control and elimination programmes, such as identifying importations and their sources, as well as areas of persistence and routes of virus movement, including transboundary incursions. This system and the tools developed should be useful for coordinating and targeting control programmes and monitoring progress as countries work towards eliminating dog-mediated rabies, as well as having potential for broader application to the surveillance of other viruses.

The Comparison of Full G and N Gene Sequences From Turkish Rabies Virus Field Strains.

Atıcı, Y., Oğuzoğlu, T.
26-04-2022
Virus Res
https://pubmed.ncbi.nlm.nih.gov/35487366

The rabies infection is a zoonotic viral disease in humans and is spread by both wild and domestic carnivores. This study aimed to molecularly characterize the field strains of the rabies virus circulating in Turkey between 2013 and 2020. Brain samples obtained from 16 infected animals (8 cattle, one donkey, three foxes, three dogs, and one marten) were tested. Full nucleoprotein (N) and glycoprotein (G) gene sequences were used to determine the genetic and antigenic characteristics of the rabies virus field strains. The phylogenetic analyses revealed that the 16 field strains identified in Turkey belonged to the Cosmopolitan lineage.

Rabies shows how scale of transmission can enable acute infections to persist at low prevalence.

Mancy, R., Rajeev, M., Lugelo, A., Brunker, K., Cleaveland, S., Ferguson, E., Hotopp, K., Kazwala, R., Magoto, M., Rysava, K., Haydon, D., Hampson, K.
28-04-2022
Science
https://doi.org/10.1126/science.abn0713

How acute pathogens persist and what curtails their epidemic growth in the absence of acquired immunity remains unknown. Canine rabies is a fatal zoonosis that circulates endemically at low prevalence among domestic dogs in low- and middle-income countries. We traced rabies transmission in a population of 50,000 dogs in Tanzania from 2002 to 2016 and applied individual-based models to these spatially resolved data to investigate the mechanisms modulating transmission and the scale over which they operate. Although rabies prevalence never exceeded 0.15%, the best-fitting models demonstrated appreciable depletion of susceptible animals that occurred at local scales because of clusters of deaths and dogs already incubating infection. Individual variation in rabid dog behavior facilitated virus dispersal and cocirculation of virus lineages, enabling metapopulation persistence. These mechanisms have important implications for prediction and control of pathogens that circulate in spatially structured populations.

Epidemiology of rabies immune globulin use in paediatric and adult patients in the USA: a cross-sectional prevalence study.

Burke, R., Russo, P., Sicilia, M., Wolowich, W., Amega, N., Nguyen, H.
26-04-2022
BMJ Open
https://pubmed.ncbi.nlm.nih.gov/35473745/

Objectives: To compare the epidemiology of paediatric and adult patients receiving rabies immune globulin (RIG). Design: Cross-sectional prevalence study. Setting: Eligible participants from the Symphony Integrated Dataverse presenting between 2013 and 2019. Participants: All adult and paediatric patients with integrated claims and demographic data associated with RIG use from the Symphony Integrated Dataverse from 2013 to 2019. Primary and secondary outcome measures: Prevalence of diagnoses and procedures associated with paediatric and adult patient population based on frequency of International Classification of Diseases (ICD-9/ICD-10) and Current Procedural Terminology codes, respectively. Methods: We used mutual information to identify features that differentiate the paediatric from adult patient population. Prevalence ratios were calculated to compare adult and paediatric patients. Results: There were 79766 adult and 20381 paediatric patients who met the inclusion criteria. Paediatric patients had a 5.92-fold higher prevalence of 'open wounds to the head; neck; and trunk', 3.10-fold higher prevalence of 'abrasion or friction burn of face; neck; and scalp except eye; without mention of infection', 4.44-fold higher prevalence of 'open wound of scalp; without mention of complication' and 6.75-fold higher prevalence of 'laceration of skin of eyelid and periocular area | laceration of eyelid involving lacrimal passages'. Paediatric patients had a 3.83-fold higher prevalence of complex repairs compared with adult patients (n=157, 0.7% vs n=157, 0.2%, respectively). Conclusions: Paediatric patients represent a significant proportion of the patient population receiving RIG, and are associated with higher prevalence of codes reporting repair of larger, more complex wounds in highly innervated anatomical regions. Dosing and administration of RIG must be informed

by animal bite wound characteristics; clinicians should understand the differences between presentations in adults and children and treat accordingly.

Genome Sequences of Five Indian Canine Rabies Virus Isolates Obtained Using Oxford Nanopore Technologies Sequencing.

Kumar, A., Nath, S., Sridhar Sudarshan, A., Iyer, V., Jadeja, N., Panchamia, N., Banerji, I., Vanak, A., Tatu, U.
26-04-2022
Microbiol Resour Announc
https://doi.org/10.1128/mra.01246-21

We report five canine rabies virus genome sequences from India that were obtained from brain samples using Oxford Nanopore Technologies sequencing. The sequences will facilitate understanding of the evolution and transmission of rabies.

Preparing liberia for rabies control: Human-dog relationship and practices, and vaccination scenarios.

Voupawoe, G., Anthony, W., Hattendorft, J., Odermatt, P., Zinsstag, J., Mauti, S.
06-02-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35139326

To reach zero dog-related human rabies deaths by 2030, Liberia must prioritize rabies as a public health threat. Understanding dog demography parameters are imperative and sets the basis for planning cost-effective and sustainable mass dog vaccination programs nationwide. We conducted a cross-sectional household survey in eleven rural districts of Bong and one urban district of Montserrado County to gather baseline information on the canine population, human-mediated dog movements, people's relationships and practices towards dogs, and further information to estimate costs for a nationwide campaign. In total, 1282 respondents were interviewed (612 rural and 670 urban). About 34% of the rural and 37% of the urban households owned at least one dog. The canine: human ratios were 1:6.1 in the rural and1:5.6 in the urban area and did not differ notably among both counties. The estimated canine population for Liberia is 594,640. The majority of respondents (55%) reported poor waste disposal. Muslims were less likely to own a dog than Christians (39% vs 19% OR: 0.4 95% CI: 0.2-0.6) (p< 0.001). Six percent of respondents mentioned that a family member was exposed to a dog bite in the past year, and most victims were adult males. Four of the victims reportedly died after showing rabies compatible symptoms. Twenty-seven percent of dog-owning households in rural areas reported that at least one dog originated from urban areas, and 2% of urban households brought in dogs from another country. In addition, 43% of respondents consumed dog meat at least once. Fifty percent of the respondents claimed knowledge of rabies but only 5.7% and 1.9% mentioned rabies transmission through rabies-infected saliva and rabies-infected mucus on broken skin. Forty percent of the respondents did not know whether rabies was incurable in humans once clinical signs appear. Assuming 30 vaccinators could vaccinate 50 dogs per day for eighteen months (371 working days), the total cost for the vaccination of the national Liberian canine population is estimated at 1.6 million (USD) for one vaccination round. Our study reveals an overall poor disease knowledge and the potential for spread of rabies in the study areas. A nationwide rabies awareness is crucial to enhance rabies prevention and control through mass dog vaccination.

Monosynaptic rabies virus tracing from projection-targeted single neurons.

Masaki, Y., Yamaguchi, M., Takeuchi, R., Osakada, F.
31-01-2022
Neurosci Res
https://pubmed.ncbi.nlm.nih.gov/35101519

A single neuron integrates inputs from thousands of presynaptic neurons to generate outputs. Circuit tracing using G-deleted rabies virus (RVΔG) vectors permits the brain-wide labeling of presynaptic inputs to targeted single neurons. However, the experimental procedures are complex, and the success rate of circuit labeling is low because of the lack of validation to increase the accuracy and efficiency of monosynaptic RVΔG tracing from targeted single neurons. We established an efficient RVΔG tracing method from projection target-defined single neurons using TVA950, a transmembrane isoform of TVA receptors, for initial viral infection. Presynaptic neurons were transsynaptically labeled from 80 % of the TVA950-expressing single starter neurons that survived after infection with EnvA-pseudotyped RVΔG in the adult mouse brain. We labeled single neuronal networks in the primary visual cortex (V1) and higher visual areas, namely the posteromedial area (PM) and anteromedial area (AM), as well as the single neuronal networks of PM-projecting V1 single neurons. Monosynaptic RVΔG tracing from projection-targeted single neurons revealed the input-output organization of single neuronal networks. Single-neuron network analysis based on RVΔG tracing will help dissect the heterogeneity of neural circuits and link circuit motifs and large-scale networks across scales, thereby clarifying information processing and circuit computation in the brain.

Dendrimer nanoplatforms for veterinary medicine applications: A concise overview.

Revue de littérature

Mignani, S., Shi, X., Rodrigues, J., Tomás, H., Majoral, J.
06-01-2022
Drug Discov Today
https://pubmed.ncbi.nlm.nih.gov/34999213

Within the nanoparticle (NP) space, dendrimers are becoming increasingly important in the field of nanomedicine, not only to treat human diseases, but also in veterinary medicine, which represents a new therapeutic approach. Major

applications include using dendrimers to tackle highly contagious foot-and-mouth disease virus (FMDV) and swine fever virus (SFV) in pigs, FMDV in cattle, hypothermic circulatory arrest (HCA) in dogs, rabies, and H9N2 avian influenza virus in chickens. As we review here, intramuscular (im) subcutaneous (sc), intravenous (iv), and intraperitoneal (ip) routes of administration can be used for the successful application of dendrimers in animals.

TRACHOME

Prevalence of Trachoma from 66 Impact Surveys in 52 Woredas of Southern Nations, Nationalities and Peoples' and Sidama Regions of Ethiopia, 2017-2019.

Seyum, D., Fetene, N., Kifle, T., Negash, H., Kabeto, T., Gebre, M., Data, T., Tadele, T., Abayo, G., Wondimu, A., Butcher, R., Bakhtiari, A., Willis, R., Boyd, S., Jimenez, C., Negussu, N., Tadesse, F., Kebede, F., Dejene, M., Solomon, A., Harding-Esch, E., Sisay, A.
27-04-2022
Ophthalmic Epidemiol
https://doi.org/10.1080/09286586.2022.2065313

Purpose: Trachoma is endemic in Southern Nations, Nationalities and Peoples' (SNNP) and Sidama regions of Ethiopia. We aimed to measure the prevalence of trachomatous inflammation - follicular (TF) among children aged 1 - 9 years and the prevalence of trachomatous trichiasis (TT) unknown to the health system among people aged ≥15 years following interventions for trachoma in 52 woredas of SNNP and Sidama regions. Methods: From 2017 - 2019, 66 two-stage cluster sampling cross-sectional population-based surveys were carried out in 52 woredas (third-level administrative divisions) using a standardized World Health Organization-recommended survey methodology. This included one impact survey in 40 woredas, two consecutive impact surveys in 10 woredas and three consecutive impact surveys in two woredas. Water, sanitation and Hygiene (WASH) access was assessed using a modified version of the United Nations Children's Fund/WHO Joint Monitoring Programme questionnaire. Results: By the end of this survey series, 15 (23%) of the woredas had met the active trachoma elimination threshold (TF prevalence <5%) and 12 (18%) had met the TT threshold (TT ≤ 0.2%). Regarding WASH coverage, 20% of households had access to an improved drinking water source within a 30-min journey and 3% had an improved latrine. There was strong evidence that TF was less common in 4 - 6-year-olds and 7 - 9-year-olds than 1 - 3-year-olds. Conclusion: Based on the findings, further antibiotic mass drug administration is required in 37 woredas and active TT case finding is needed in 40 woredas. In these surveys, access to WASH facilities was very low; WASH improvements are required.

Chlamydia trachomatis: quest for an eye-opening vaccine breakthrough.

Chavda, V., Pandya, A., Kypreos, E., Patravale, V., Apostolopoulos, V.
26-04-2022
Expert Rev Vaccines
https://doi.org/10.1080/14760584.2022.2061461

Introduction: *Chlamydia trachomatis,* commonly referred to as chlamydia (a bacterium), is a common sexually transmitted infection, and if attended to early, it can be treatable. However, if left untreated it can lead to serious consequences. *C. trachomatis* infects both females and males although its occurrence in females is more common, and it can spread to the eyes causing disease and in some case blindness. Area covered: With ongoing attempts in the most impoverished regions of the country, trachoma will be eradicated as a blinding disease by the year 2022. A prophylactic vaccine candidate with established safety and efficacy is a cogent tool to achieve this goal. This manuscript covers the vaccine development programs for chlamydial infection. Expert opinion: Currently, the Surgery Antibiotics Facial Environmental (SAFE) program is being implemented in endemic countries in order to reduce transmission and control of the disease. Vaccines have been shown over the years to protect against infectious diseases. Charge variant-based adjuvant can also be used for the successful delivery of chlamydial specific antigen for efficient vaccine delivery through nano delivery platform. Thus, a vaccine against *C. trachomatis* would be of great public health benefit.

Atypical Corneal Phenotype in Patients With Trachoma and Secondary Amyloidosis.

Gupta, N., Yadav, S., Solomon, A., Jain, S., Kashyap, S., Vanathi, M., Tandon, R.
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Cornea
https://doi.org/10.1097/ICO.0000000000002791

Purpose: To report clinical presentation, in vivo confocal microscopic features, and corneal phenotype in patients with trachomatous keratopathy (TK) and secondary amyloidosis. Methods: Histopathological records of all patients undergoing keratoplasty at the Dr. Rajendra Prasad Centre for Ophthalmic Sciences over a 3-year period were scanned retrospectively for a diagnosis of TK and amyloidosis. Demographic profile and details of preoperative comprehensive ophthalmic assessment were extracted. The histopathology was freshly reviewed. Results: Fifteen patients (29 eyes) with TK and atypical corneal involvement due to amyloid deposition were identified. Herbert's pits and upper palpebral conjunctival scarring were present in all cases. Central or total diffuse corneal scarring was present involving the anterior stroma in 5 (31%) and the full thickness of the cornea in 11 (69%) of the eyes. Eight (73%) of 11 patients with deep stromal amyloid deposits revealed bilateral, discrete, blue-white opacities at the level of deep stroma and Descemet membrane (DM). Endothelial cells were atrophic and flattened with gutta formation. Confoscans

revealed hyperreflective, needle-shaped crystalline deposits of extracellular amyloid at various depths of the corneal stroma up to DM. All host corneal buttons demonstrated Congo red-positive amyloid deposits on histopathological examination. **Conclusions:** We describe a distinct form of TK unlike the usual presentation of dense, leucomatous, vascularized corneal scarring in trachoma. We believe that amyloid deposits in DM and the corneal endothelium have not previously been reported in patients with trachoma.

ULCERE DE BURULI

PIAN

LEPRE

A comprehensive analysis of the circRNA-miRNA-mRNA network in osteocyte-like cell associated with Mycobacterium leprae infection.

Gao, Z., Liu, Q., Zhao, J., Zhao, Y., Tan, L., Zhang, S., Zhou, Y., Chen, Y., Guo, Y., Feng, Y.
02-05-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010379

Background: Bone formation and loss are the characteristic clinical manifestations of leprosy, but the mechanisms underlying the bone remodeling with Mycobacterium leprae (M. leprae) infection are unclear. **Methodology/Principal findings:** Osteocytes may have a role through regulating the differentiation of osteogenic lineages. To investigate osteocyte-related mechanisms in leprosy, we treated osteocyte-like cell with N-glycosylated muramyl dipeptide (N.g MDP). RNA-seq analysis showed 724 differentially expressed messenger RNAs (mRNAs) and 724 differentially expressed circular RNA (circRNAs). Of these, we filtered through eight osteogenic-related differentially expressed genes, according to the characteristic of competing endogenous RNA, PubMed databases, and bioinformatic analysis, including TargetScan, Gene Ontology, and Kyoto Encyclopedia of Genes and Genomes. Based on these results, we built a circRNA-microRNA (miRNA)-mRNA triple network. Quantitative reverse-transcription polymerase chain reaction and western blots analyses confirmed decreased Clock expression in osteocyte-like cell, while increased in bone mesenchymal stem cells (BMSCs), implicating a crucial factor in osteogenic differentiation. Immunohistochemistry showed obviously increased expression of CLOCK protein in BMSCs and osteoblasts in N.g MDP-treated mice, but decreased expression in osteocytes. **Conclusions/Significance:** This analytical method provided a basis for the relationship between N.g MDP and remodeling in osteocytes, and the circRNA-miRNA-mRNA triple network may offer a new target for leprosy therapeutics.

Dapsone induced hemolysis in a patient with Hansen's disease and G6PD deficiency: A preventable peril.

Ghorui, A., Patra, P.
26-04-2022
Clin Case Rep
https://doi.org/10.1002/ccr3.5700

Although under-reported, hemolytic anemia is common with dapsone-containing regimen in leprosy. It is prudent to screen for underlying G6PD deficiency in boys before administering dapsone to prevent potentially life-threatening episode of intravascular hemolysis in children with leprosy.

Guiding policy towards zero leprosy: Challenges for modelling & economic evaluation.

Blok, D., de Vlas, S.
29-04-2022
Indian J Med Res
https://doi.org/10.4103/ijmr.ijmr_220_22

Zero leprosy: A united effort using existing & new tools but new perspectives.

van Brakel, W.
29-04-2022
Indian J Med Res
https://doi.org/10.4103/ijmr.ijmr_14_22

Ultrasonography as a diagnostic tool for Neural Pain in Leprosy.

Spitz, C., Mogami, R., Pitta, I., Hacker, M., Sales, A., Sarno, E., Jardim, M.
29-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010393

Leprosy is still a prevalent disease in Brazil, representing 93% of all occurrences in the Americas. Leprosy neuropathy is one of the most worrying manifestations of the disease. Acute neuropathy usually occurs during reaction episodes and is called neuritis. Twenty-two leprosy patients were included in this study. These patients had neural pain associated with ulnar sensory neuropathy, with or without adjunct motor involvement. The neurological picture began within thirty days of the clinical evaluation. The patients underwent a nerve conduction study and the demyelinating findings confirmed

the diagnosis of neuritis. Ultrasonographic study (US) of the ulnar nerve was performed in all patients by a radiologist who was blinded to the clinical or neurophysiological results. Morphological characteristics of the ulnar nerve were analyzed, such as echogenicity, fascicular pattern, transverse cross-sectional area (CSA), aspect of the epineurium, as well as their anatomical relationships. The volume of selected muscles referring to the ulnar nerve, as well as their echogenicity, was also examined. Based on this analysis, patients with increased ulnar nerve CSA associated with loss of fascicular pattern, epineurium hyperechogenicity and presence of power Doppler flow were classified as neuritis. Therefore, patients initially classified by the clinical-electrophysiological criteria were reclassified by the imaging criteria pre-established in this study as with and without neuritis. Loss of fascicular pattern and flow detection on power Doppler showed to be significant morphological features in the detection of neuritis. In 38.5% of patients without clinical or neurophysiological findings of neuritis, US identified power Doppler flow and loss of fascicular pattern. The US is a method of high resolution and portability, and its low cost means that it could be used as an auxiliary tool in the diagnosis of neuritis and its treatment, especially in basic health units.

Drug resistance in leprosy: an update following 70 years of chemotherapy.

Revue de littérature

Aubry, A., Sammarco Rosa, P., Chauffour, A., Lee Fletcher, M., Cambau, E., Avanzi, C.
25-04-2022
Infect Dis Now
https://pubmed.ncbi.nlm.nih.gov/35483633

Leprosy is one of the oldest infectious diseases, reported for more than 2,000 years. Leprosy elimination goal as a public health problem set by the World Health Organization, aiming for a global prevalence rate <1 patient in a population of 10,000, was achieved in 2000 mainly thanks to the worldwide use of leprosy drugs starting in the 1980s and their access at no cost for patients since 1995. However, around 200,000 new cases are still reported each year, particularly in India, Brazil, and Indonesia. As with other bacteria of medical interest, antimicrobial resistance is observed in Mycobacterium leprae strains in several parts of the world, despite multidrug therapy being the recommended standard leprosy treatment to avoid resistance selection since 1982. Therefore, identifying and monitoring resistance is necessary. We provide an overview of the historical facts that led to the current drug resistance situation, the antibiotics effective against M. leprae, their mechanisms of action and resistance, and resistance detection methods. We also discuss therapeutic management of the resistant cases, new genes with potential roles in drug resistance and bacterial adaptation, new drugs under investigation, and the risk for resistance selection with the chemoprophylaxis measures.

A critical appraisal of the ENLIST severity scale for erythema nodosum leprosum.

Kumar, B., Mehta, H., Narang, T., Dogra, S.
26-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010378

Mycobacterium lepromatosis as Cause of Leprosy, Colombia.

Cardona-Castro, N., Escobar-Builes, M., Serrano-Coll, H., Adams, L., Lahiri, R.
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Emerg Infect Dis
https://doi.org/10.3201/eid2805.212015

Leprosy is a granulomatous infection caused by infection with Mycobacterium leprae or M. lepromatosis. We evaluated skin biopsy and slit skin smear samples from 92 leprosy patients in Colombia by quantitative PCR. Five (5.4%) patients tested positive for M. lepromatosis, providing evidence of the presence of this pathogen in Colombia.

The effect of conditional cash transfers on the control of neglected tropical disease: a systematic review.

Ahmed, A., Aune, D., Vineis, P., Pescarini, J., Millett, C., Hone, T.
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Lancet Glob Health
https://pubmed.ncbi.nlm.nih.gov/35427521

Background: Neglected tropical diseases (NTDs) are diseases of poverty and affect 1·5 billion people globally. Conditional cash transfer (CCTs) programmes alleviate poverty in many countries, potentially contributing to improved NTD outcomes. This systematic review examines the relationship between CCTs and screening, incidence, or treatment outcomes of NTDs. Methods: In this systematic review we searched MEDLINE, Embase, Lilacs, EconLit, Global Health, and grey literature websites on Sept 17, 2020, with no date or language restrictions. Controlled quantitative studies including randomised controlled trials (RCTs) and observational studies evaluating CCT interventions in low-income and middle-income countries were included. Any outcome measures related to WHO's 20 diseases classified as NTDs were included. Studies from high-income countries were excluded. Two authors (AA and TH) extracted data from published studies and appraised risk of biases using the Risk of Bias in Non-Randomised Studies of Interventions and Risk of Bias 2 tools. Results were analysed narratively. This study is registered with PROSPERO, CRD42020202480. Findings: From the search, 5165 records were identified; of these, 11 studies were eligible for inclusion covering four CCTs in Brazil, the Philippines, Mexico, and Zambia. Most studies were either RCTs or quasi-experimental studies and ten were assessed to be of moderate quality. Seven studies reported improved NTD outcomes associated with CCTs, in particular, reduced incidence of leprosy and increased uptake of deworming

treatments. There was some evidence of greater benefit of CCTS in lower socioeconomic groups but subgroup analysis was scarce. Methodological weaknesses include self-reported outcomes, missing data, improper randomisation, and differences between CCT and comparator populations in observational studies. The available evidence is currently limited, covering a small proportion of CCTs and NTDs. **Interpretation:** CCTs can be associated with improved NTD outcomes, and could be driven by both improvements in living standards from cash benefits and direct health effects from conditionalities related to health-care use. This evidence adds to the knowledge of health-improving effects from CCTs in poor and vulnerable populations. **Funding:** None.

Neglected tropical rheumatic diseases.

Revue de littérature

Sahoo, R., Wakhlu, A., Agarwal, V.
10-02-2022
Clin Rheumatol
https://doi.org/10.1007/s10067-022-06090-6

The complexities of dealing with rheumatic diseases in tropical countries are diverse and likely due to limited health care infrastructure, lack of diagnostic and therapeutic facilities, impact of dominant prevailing diseases, and the challenges of differentiating from infectious and non-infectious disease mimics. Several tropical diseases present with musculoskeletal and rheumatic manifestations and often pose a diagnostic dilemma to rheumatologists. The diagnosis is often delayed or the disease is misdiagnosed, leading to poor patient outcomes. Endemic tropical diseases like tuberculosis and leprosy have myriad rheumatic presentations and remain important differentials to consider in patients with rheumatic manifestations. Infection with human immunodeficiency virus is a great masquerade and can mimic manifestations of multiple diseases. The role of viral infections in triggering and perpetuating autoimmunity is well known and chikungunya arthritis is a classic example of the same. This review highlights the rheumatic manifestations of tropical diseases and aims to create awareness among the caregivers. Key Points • It is crucial to be aware and identify infectious diseases presenting with rheumatic manifestations in the tropics. • Presentations akin to classic rheumatic syndromes such as rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus and vasculitis are common.

Impact of the COVID-19 pandemic on the diagnosis of leprosy in Brazil: An ecological and population-based study.

da Paz, W., Souza, M., Tavares, D., de Jesus, A., Dos Santos, A., do Carmo, R., de Souza, C., Bezerra-Santos, M.
15-01-2022
Lancet Reg Health Am
https://doi.org/10.1016/j.lana.2021.100181

Background: The pandemic caused by COVID-19 has seriously affected global health, resulting in the suspension of many regular health services, making the diagnosis of other infections difficult. Therefore, this study aimed to assess the impact of the COVID-19 pandemic on the diagnosis of leprosy in Brazil during the year 2020. **Methods:** We evaluated the monthly incidence of leprosy and calculated the percentage change to verify whether there was an increase or decrease in the number of leprosy cases in 2020, considering the monthly average of cases over the previous 5 years. We used interrupted time series analysis to assess the trend in the diagnosis of leprosy before and after the start of COVID-19 in Brazil and prepared spatial distribution maps, considering the percentage variation in each state. **Findings:** We verified a reduction of 41.4% of leprosy cases in Brazil in 2020. Likewise, there was a reduction of leprosy notifications in children under 15 years-old (-56.82%). Conversely, the diagnosis of multibacillary leprosy increased (8.1%). There was a decreasing trend in the leprosy incidence in the general population between 2015 and 2020 in Brazil. Spatial distribution maps depicted a reduction of up to 100% in new cases of leprosy in some states. **Interpretation:** Along with COVID-19 spread there was a reduction in leprosy diagnosis in the general population and children under 15 years-old, and also an increase in multibacillary cases diagnosed, signalling a serious impact of the pandemic on leprosy control strategies in Brazil. **Funding:** This research received no specific grants.

Efficacy of fluorescent microscopy versus modified Fite-Faraco stain in skin biopsy specimens of leprosy cases - a comparative study.

Kalagarla, S., Alluri, R., Saka, S., Godha, V., Undavalli, N., Kolalapudi, S.
21-01-2022
Int J Dermatol
https://doi.org/10.1111/ijd.16046

Background: Histopathological examination of skin remains the cornerstone in the diagnosis of leprosy. At a few centers, fluorescent microscopy has been found to be useful in detecting more acid-fast bacilli (AFB) compared to modified Fite-Faraco staining but is sparsely documented. Hence, we studied the sensitivity of fluorescent microscopy and modified Fite-Faraco stain in the detection of Mycobacterium leprae in tissue sections. **Methods:** Patients attending our outpatient department during January 2019 to June 2020 with the clinical features of leprosy were examined, and the diagnosis was confirmed by histopathology after informed consent. Tissue sections were stained by fluorescent stain and modified Fite-Faraco stain. Bacillary index was calculated for each case. **Results:** Forty patients were recruited after following the inclusion and exclusion criteria. AFB were demonstrated in 20 patients by modified Fite-Faraco stain and in 27 patients with fluorescent stain. The sensitivity of fluorescent staining method (67.5%) was higher than modified Fite-Faraco stain (50%). Bacillary index was increased in 26 out of 40 cases by the fluorescent staining compared to the modified Fite-Faraco staining. Chi-square value was 69.3 and P value was 0.000, indicating a statistically significant correlation. **Limitations:** Fluorescent microscope is expensive, and trained people are

needed to identify the bacilli. **Conclusion:** Fluorescent staining is more sensitive than modified Fite-Faraco staining in the detection of AFB in tissue sections. The bacilli detected per field were high with the fluorescent staining compared to the modified Fite-Faraco method.

Leprosy Relapse: A Retrospective Study on Epidemiologic, Clinical, and Therapeutic Aspects at a Brazilian Referral Center.

Nascimento, A., Dos Santos, D., Antunes, D., Gonçalves, M., Santana, M., Dornelas, B., Goulart, L., Goulart, I.
10-01-2022
Int J Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35017109

Objectives: We aimed to characterize the profile of patients diagnosed with leprosy relapse and understand the influence of different multidrug therapy (MDT) treatments and initial disease presentation. **Methods:** This retrospective study included patients diagnosed with leprosy relapse at a referral center in Brazil from 2013 to 2018. We analyzed their clinico-epidemiologic characteristics, laboratory data, and bacilloscopic tests. Survival analysis was used to determine the time elapsed until relapse according to the previous treatment and clinical forms of the disease. **Results:** A total of 126 cases of relapse were analyzed, which comprised 11.89% (126/1059) of the cases. The median time elapsed until a relapse was 10 years, and most patients had previously undergone 12 doses of MDT (40.48%; 51/126). Undergoing 24 doses of MDT was associated with a better prognosis regarding relapse over time compared with 6 or 12 doses of MDT therapy. Most cases of relapse were classified as multibacillary (96.03%; 121/126). **Conclusion:** The incidence of relapse was greater than observed in other studies. The high percentage of multibacillary patients who had negative bacillary indices demonstrated that the bacillary index cannot be considered to be an essential criterion for relapse, especially concerning making an early diagnosis.

Trigger of Type 2 Lepra reaction with acute foot drop following Covid-19 vaccination.

Panda, A., Begum, F., Panda, M., Jena, A.
25-01-2022
J Eur Acad Dermatol Venereol
https://doi.org/10.1111/jdv.17915

TRYPANOSOMES (TRYPANOSOMIASE ET MALADIE DE CHAGAS)

In vitro effects and mechanisms of action of *Bidens pilosa* in *Trypanosoma brucei*.

Dofuor, A., Djameh, G., Amoa-Bosompem, M., Kwain, S., Osei, E., Tetevi, G., Ayertey, F., Bolah, P., Okine, L., Kyeremeh, K., Gwira, T., Ohashi, M.
11-08-2021
J Tradit Complement Med
https://doi.org/10.1016/j.jtcme.2021.08.008

Background and aim: African trypanosomiasis poses serious health and economic concerns to humans and livestock in several sub-Saharan African countries. The aim of the present study was to identify the antitrypanosomal compounds from *B. pilosa* (whole plant) through a bioactivity-guided isolation and investigate the *in vitro* effects and mechanisms of action against *Trypanosoma brucei* (*T. brucei*). **Experimental procedure:** Crude extracts and fractions were prepared from air-dried pulverized plant material of *B. pilosa* using the modified Kupchan method of solvent partitioning. The antitrypanosomal activities of the fractions were determined through cell viability analysis. Effects of fractions on cell death and cell cycle of *T. brucei* were determined using flow cytometry, while fluorescence microscopy was used to investigate alterations in cell morphology and distribution. **Results and conclusion:** The solvent partitioning dichloromethane (BPFD) and methanol (BPFM) fractions of *B. pilosa* exhibited significant activities against *T. brucei* with respective half-maximal inhibitory concentrations (IC_{50}s) of 3.29 μg/ml and 5.86 μg/ml and resulted in the formation of clumpy subpopulation of *T. brucei* cells. Butyl (compound **1**) and propyl (compound **2**) esters of tryptophan were identified as the major antitrypanosomal compounds of *B. pilosa.* Compounds **1** and **2** exhibited significant antitrypanosomal effects with respective IC_{50} values of 0.66 and 1.46 μg/ml. At the IC_{50} values, both compounds significantly inhibited the cell cycle of *T. brucei* at the G0-G1 phase while causing an increase in G2-M phase. The results suggest that tryptophan esters may possess useful chemotherapeutic properties for the control of African trypanosomiasis.

Etiological spectrum of persistent fever in the tropics and predictors of ubiquitous infections: a prospective four-country study with pooled analysis.

Bottieau, E., Van Duffel, L., El Safi, S., Koirala, K., Khanal, B., Rijal, S., Bhattarai, N., Phe, T., Lim, K., Mukendi, D., Kalo, J., Lutumba, P., Barbé, B., Jacobs, J., Van Esbroeck, M., Foqué, N., Tsoumanis, A., Parola, P., Yansouni, C., Boelaert, M., Verdonck, K., Chappuis, F.
02-05-2022
BMC Med
https://doi.org/10.1186/s12916-022-02347-8

Background: Persistent fever, defined as fever lasting for 7 days or more at first medical evaluation, has been hardly investigated as a separate clinical entity in the tropics. This study aimed at exploring the frequencies and diagnostic predictors of the ubiquitous priority (i.e., severe and treatable) infections causing persistent fever in the tropics. **Methods:** In six different health settings across four countries in Africa and Asia (Sudan, Democratic Republic of Congo [DRC], Nepal, and Cambodia), consecutive patients aged 5 years or older with

persistent fever were prospectively recruited from January 2013 to October 2014. Participants underwent a reference diagnostic workup targeting a pre-established list of 12 epidemiologically relevant priority infections (i.e., malaria, tuberculosis, HIV, enteric fever, leptospirosis, rickettsiosis, brucellosis, melioidosis, relapsing fever, visceral leishmaniasis, human African trypanosomiasis, amebic liver abscess). The likelihood ratios (LRs) of clinical and basic laboratory features were determined by pooling all cases of each identified ubiquitous infection (i.e., found in all countries). In addition, we assessed the diagnostic accuracy of five antibody-based rapid diagnostic tests (RDTs): Typhidot Rapid IgM, Test-it™ Typhoid IgM Lateral Flow Assay, and SD Bioline Salmonella typhi IgG/IgM for Salmonella Typhi infection, and Test-it™ Leptospira IgM Lateral Flow Assay and SD Bioline Leptospira IgG/IgM for leptospirosis. **Results:** A total of 1922 patients (median age: 35 years; female: 51%) were enrolled (Sudan, n=667; DRC, n=300; Nepal, n=577; Cambodia, n=378). Ubiquitous priority infections were diagnosed in 452 (23.5%) participants and included malaria 8.0% (n=154), tuberculosis 6.7% (n=129), leptospirosis 4.0% (n=77), rickettsiosis 2.3% (n=44), enteric fever 1.8% (n=34), and new HIV diagnosis 0.7% (n=14). The other priority infections were limited to one or two countries. The only features with a positive LR≥3 were diarrhea for enteric fever and elevated alanine aminotransferase level for enteric fever and rickettsiosis. Sensitivities ranged from 29 to 67% for the three RDTs targeting S. Typhi and were 9% and 16% for the two RDTs targeting leptospirosis. Specificities ranged from 86 to 99% for S. Typhi detecting RDTs and were 96% and 97% for leptospirosis RDTs. **Conclusions:** Leptospirosis, rickettsiosis, and enteric fever accounted each for a substantial proportion of the persistent fever caseload across all tropical areas, in addition to malaria, tuberculosis, and HIV. Very few discriminative features were however identified, and RDTs for leptospirosis and Salmonella Typhi infection performed poorly. Improved field diagnostics are urgently needed for these challenging infections. NCT01766830 at ClinicalTrials.gov.

Benznidazole, itraconazole, and their combination for the treatment of chronic experimental Chagas disease in dogs.

Alves Cunha, E., Vieira da Silva Torchelsen, F., da Silva Fonseca, K., Dutra Sousa, L., Abreu Vieira, P., Carneiro, C., Mauro de Castro Pinto, K., Torres, R., de Lana, M.
28-04-2022
Exp Parasitol
https://pubmed.ncbi.nlm.nih.gov/35490799

Treatment for Chagas disease has limited efficacy in the chronic phase. We evaluated benznidazole (BZ) and itraconazole (ITZ) individually and in association in dogs 16 months after infection with a BZ-resistant Trypanosoma cruzi strain. Four study groups (20 animals) were evaluated and treated for 60 days with BZ, ITZ, or BZ + ITZ, and maintained in parallel to control group infected and not treated (INT). All dogs were evaluated in the first, sixth, 12th, 18th and 24th months of study. Polymerase chain reaction (PCR) was negative in 2 of 3 animals in the BZ + ITZ group, 2 of 5 in the BZ group, and 4 of 5 in the ITZ group. Hemoculture performed in the 24th month was negative in all groups. Enzyme-linked immunoassay remained reactive in all treated animals. Echocardiography differentiated treated animals from control animals. Quantitative PCR analysis of cardiac tissue was negative in the BZ + ITZ and BZ groups, positive in 2 of 5 dogs in the ITZ group and in 2 of 3 dogs in the control group, but negative in colon tissue in all groups. Inflammation was significantly reduced in the right atrium and left ventricle of dogs treated with BZ + ITZ and BZ compared with those receiving ITZ alone. Fibrosis was absent in most dogs treated with BZ + ITZ, mild in those treated with BZ or ITZ alone, and intense in the control group. Parasitological and histopathological evaluations showed that BZ + ITZ treatment improved or stabilized the clinical condition of the dogs.

Antigenic diversity of MASP gene family of Trypanosoma cruzi.

Leão, A., Viana, L., Fortes de Araujo, F., de Lourdes Almeida, R., Freitas, L., Coqueiro-Dos-Santos, A., da Silveira-Lemos, D., Cardoso, M., Reis-Cunha, J., Teixeira-Carvalho, A., Bartholomeu, D.
26-04-2022
Microbes Infect
https://pubmed.ncbi.nlm.nih.gov/35487471

Trypanosoma cruzi, the etiological agent of Chagas disease (CD), is a heterogeneous species with high genetic and phenotypic diversity. MASP is the second largest multigene family of T. cruzi. The high degree of polymorphism of the family associated with its location at the surface of infective forms of T. cruzi suggests that MASP participates in mechanisms of host-parasite interaction. In this work, MASP members were divided into 7 subgroups based on protein sequence similarity, and one representative member from each subgroup was chosen to be expressed recombinantly. Immunogenicity of recombinant MASP proteins (rMASP) was investigated using different sera panels from T. cruzi infected mice. To mimic a natural condition in which different MASP members are expressed at the same time in the parasite population, a multiplex bead-based flow cytometry assay was also standardized. Results showed that rMASPs are poorly recognized by sera from mice infected with Colombiana strain, whereas sera from mice infected with CL Brener and Y display high reactivity against the majority of rMASPs tested. Flow cytometry showed that MASP recognition profile changes 10 days after infection. Also, multiplex assay suggests that MASP M1 and M2 are more immunogenic than the other MASP members evaluated that may play an immunodominant role during infection.

Essential oils from different Myrtaceae species from Brazilian Atlantic Forest biome - chemical dereplication and evaluation of antitrypanosomal activity.

Maiolini, T., Rosa, W., Miranda, D., Costa-Silva, T., Tempone, A., Bueno, P., Dias, D., Chagas de Paula, D., Sartorelli, P., Lago, J., Soares, M.
29-04-2022
Chem Biodivers
https://doi.org/10.1002/cbdv.202200198

Chagas Disease (CD), caused by flagellate protozoan Trypanosoma cruzi, is a Neglected Tropical Diseases (NTD) that affect approximately seven million people worldwide with a restrict therapeutical arsenal. In the present study, the essential oils from 18 Myrtaceae species were extracted, chemically dereplicated, and evaluated in vitro against T. cruzi. From these, eight essential oils were considered promising (IC50 < 10 μg/mL and SI > 10) against the protozoan: Eugenia florida, E. acutata, E. widgrenii, Calyptranthes brasilienses, C. widgreniana, Plinia cauliflora, Campomanesia xanthocarpa, and Psidium guajava. Multivariate data analysis pointed out (E)-caryophyllene, α-humulene, limonene, caryophyllene oxide, and α-copaene playing an important role in the anti-T. cruzi activity. The obtained results demonstrated the potential of essential oils of Myrtaceae species as valuable sources of bioactive compounds against T. cruzi.

Essential Bromodomain *Tc*BDF2 as a Drug Target against Chagas Disease.

Pezza, A., Tavernelli, L., Alonso, V., Perdomo, V., Gabarro, R., Prinjha, R., Rodríguez Araya, E., Rioja, I., Docampo, R., Calderón, F., Martin, J., Serra, E.
28-04-2022
ACS Infect Dis
https://doi.org/10.1021/acsinfecdis.2c00057

Trypanosoma cruzi is a unicellular parasite that causes Chagas disease, which is endemic in the American continent but also worldwide, distributed by migratory movements. A striking feature of trypanosomatids is the polycistronic transcription associated with post-transcriptional mechanisms that regulate the levels of translatable mRNA. In this context, epigenetic regulatory mechanisms have been revealed to be of great importance, since they are the only ones that would control the access of RNA polymerases to chromatin. Bromodomains are epigenetic protein readers that recognize and specifically bind to acetylated lysine residues, mostly at histone proteins. There are seven coding sequences for BD-containing proteins in trypanosomatids, named *Tc*BDF1 to *Tc*BDF7, and a putative new protein containing a bromodomain was recently described. Using the Tet-regulated overexpression plasmid p*Tc*INDEX-GW and CRISPR/Cas9 genome editing, we were able to demonstrate the essentiality of *Tc*BDF2 in *T. cruzi*. This bromodomain is located in the nucleus, through a bipartite nuclear localization signal. *Tc*BDF2 was shown to be important for host cell invasion, amastigote replication, and differentiation from amastigotes to trypomastigotes. Overexpression of *Tc*BDF2 diminished epimastigote replication. Also, some processes involved in pathogenesis were altered in these parasites, such as infection of mammalian cells, replication of amastigotes, and the number of trypomastigotes released from host cells. In *in vitro* studies, *Tc*BDF2 was also able to bind inhibitors showing a specificity profile different from that of the previously characterized *Tc*BDF3. These results point to *Tc*BDF2 as a druggable target against *T. cruzi*.

Trypanosoma brucei brucei Induced Hypoglycaemia Depletes Hepatic Glycogen and Altered Hepatic Hexokinase and Glucokinase Activities in Infected Mice.

Ojo, R., Paul, G., Magellan, D., Dangara, D., Gyebi, G.
27-04-2022
Acta Parasitol
https://doi.org/10.1007/s11686-022-00550-4

Purpose: Little progress has been made in understanding the effect of Trypanosoma brucei brucei infection that was allowed to run its course without treatment on human and animal carbohydrate metabolism even though most of the symptoms associated with the disease can be clearly linked with interference with host energy generation. The present study therefore assessed the course of untreated Trypanosoma brucei brucei infection on hepatic glycogen, hepatic hexokinase and glucokinase activities. Methods: Mice were grouped into two: control and infected group. Trypanosomiasis was induced by intraperitoneal inoculation of 1×10^4 parasites/mice in 0.3 ml of phosphate saline glucose. The infection was allowed to run its course until the first mortality was recorded with all the mice showing chronic symptoms of the second stage of the disease before the research was terminated. Blood and liver samples were collected from the mice in each group for the assessment of hepatic glycogen and total protein, hepatic hexokinase and glucokinase activities, liver biomarkers, blood glucose and protein with packed cell volume. Results: The infection resulted in decrease in blood glucose, hepatic glycogen, liver protein, PCV, hepatic hexokinase and glucokinase activities, but increase in serum total protein and liver biomarkers. Conclusion: Trypanosomiasis negatively affects hepatic integrity, resulting in the depletion of hepatic glycogen content and suppression of both hepatic hexokinase and glucokinase activities. The suppression of hepatic hexokinase and glucokinase activities suggested that trypanosomiasis affected the oxidation of glucose and host energy generation via glycolysis. This probably denied the host of the needed energy which is likely the reason for early death in untreated African trypanosomiasis.

3D Fib-sem structural insights into the architecture of sub-pellicular microtubules of trypanosoma cruzi epimastigotes.

Vidal, J., De Souza, W.
27-04-2022
Biol Cell
https://doi.org/10.1111/boc.202100038

Background information: Trypanosomatidae, which includes eukaryotic species agents of diseases like leishmaniasis,

sleeping sickness and Chagas disease have special structures and organelles not found in mammalian cells. They present a layer of microtubules, known as subpellicular microtubules (SPMT), located underneath the plasma membrane and responsible for preserving cell morphology, cell polarity, the position of single copy organelles and morphological changes that occur throughout the protozoan life cycle. Even though a lot of knowledge about the SPMT is available, we still do not know exactly how each microtubule in the system is organized in three dimensions. Here, we use FIB-SEM to analyze the tridimensional organization of epimastigotes SPMT. Results: The high-resolution 3D analyses revealed that certain microtubules of the SPMT end more prematurely than the neighboring ones. Conclusions: These microtubules could (1) be shorter or (2) have the same length as the neighboring ones, assuming that those end up earlier at their other end, might be treadmilling/catastrophe events that have not yet been described in trypanosomatids. This article is protected by copyright. All rights reserved.

Study of the dynamic behavior of the cruzain enzyme in free and complexed forms with competitive and noncovalent benzimidazole inhibitors.

Reis, C., Souza, H., Leme, R., Castelo-Branco, F., Fernandes, T., Boechat, N., Dias, L., Hoelz, L.
27-04-2022
J Biomol Struct Dyn
https://doi.org/10.1080/07391102.2022.2067238

There are only two drugs for the treatment of Chagas disease, namely, nifurtimox and benznidazole, that can cause several adverse effects. Despite the effectiveness of these drugs in the disease's acute phase, they are not recognized as curative in the chronic phase, establishing the need for more effective treatment in all stages of the disease. Cruzain is an enzyme that plays a vital role in the life cycle of the etiologic agent, the protozoan T*rypanosoma cruzi,* being relevant as a therapeutic target in the planning of new drugs. Using molecular docking and dynamics simulations, we have investigated the structural and dynamic factors that can be involved in the enzyme inhibition process at the atomic-molecular level by benzimidazole compounds that are potent cruzain inhibitors with in vitro trypanocidal activity. The study suggests that these inhibitors bind cruzain through steric and hydrogen bonding interactions without altering its secondary structure content and protein compaction. Besides, we observed that these inhibitors decrease the correlation of movements between Cα-atoms of cruzain, increasing the number of atomic communities, mainly in the α-helix that presents the catalytic Cys25 residue. As expected, we also observed a correlation between the inhibitory activity of each inhibitor and their respective binding-free energies, reinforcing that the affinity of the complexes seems to be a relevant factor for enzymatic inhibition. Hence, the results presented in this work contribute to a better understanding of the cruzain enzyme inhibition mechanism through competitive and non-covalent inhibitors.Communicated by Ramaswamy H. Sarma.

Mental distress and health-related quality of life in gambiense human African trypanosomiasis: a case-control study in the Democratic Republic of Congo.

Mudji, J., Ackam, N., Amoako, Y., Madinga, B., Mumbere, P., Agbanyo, A., Blum, J., Phillips, R., Molyneux, D.
26-04-2022
Trans R Soc Trop Med Hyg
https://pubmed.ncbi.nlm.nih.gov/35474014

Background: The extent to which neuropsychiatric sequelae affects the mental health status and quality of life of former gambiense human African trypanosomiasis (gHAT) patients is not known. Methods: We assessed anxiety, depression and health-related quality of life (HRQoL) in 93 patients and their age- and sex-matched controls using the Hospital Anxiety and Depression Scale, Becks Depression Inventory and the 36-item Short Form Health Survey in structured interviews in the Vanga health zone in the Democratic Republic of Congo. Data were analysed using Stata version 14.0. The degree of association between neurologic sequelae and mental distress was evaluated using the Student's t-test and χ2 or Fisher's exact tests, where appropriate, with a p-value <0.05 deemed to be statistically significant. Results: We found that neurological sequelae persisted in former patients at least 15 y after treatment. Depression (p<0.001) and anxiety (p=0.001) were significantly higher in former patients with neurologic sequelae. The mean quality-of-life (QoL) scores were significantly lower for patients than in controls in the physical, emotional and mental health domains. Conclusions: The presence of neurological sequelae leads to mental distress and a diminished QoL in former gHAT patients. Minimising neurologic sequelae and incorporating psychosocial interventions should be essential management goals for gHAT.

Spatial meta-analysis of the occurrence and distribution of tsetse-transmitted animal trypanosomiasis in Cameroon over the last 30 years.

Sevidzem, S., Koumba, A., Mavoungou, J., Windsor, P.
27-04-2022
Epidemiol Infect
https://doi.org/10.1017/S0950268822000772

Synthesis and biological evaluation of imidamide analogs as selective anti-trypanosomal agents.

Bobba, V., Li, Y., Afrin, M., Dano, R., Zhang, W., Li, B., Su, B.
04-04-2022
Bioorg Med Chem
https://pubmed.ncbi.nlm.nih.gov/35396128

Human African trypanosomiasis is caused by a protozoan parasite Trypanosoma brucei majorly infecting people living in sub-Saharan Africa. Current limited available treatments suffer from drug resistance, severe adverse effects, low efficacy, and

costly administrative procedures in African countries with limited medical resources. Therefore, there is always a perpetual demand for advanced drug development and invention of new strategies to combat the disease. Previous work in our lab generated a library of sulfonamide analogs as selective tubulin inhibitors, based on the structural difference between mammalian and trypanosome tubulin proteins. Further lead derivatization was performed in the current study and generated 25 potential drug candidates to improve the drug efficacy and uptake by selectively targeting the parasite's P2 membrane transporter protein with imidamide moiety. One of the newly synthesized analogs, compound 25 with a di-imidamide moiety, has shown greater potency with an IC_{50} of 1 nM to selectively inhibit the growth of trypanosome cells without affecting the viability of mammalian cells. Western blot analyses reveal that the compound suppressed tubulin polymerization in T. brucei cells. A detailed structure-activity relationship (SAR) was summarized that will be used to guide future lead optimization.

Thiosemicarbazone derivatives: Evaluation as cruzipain inhibitors and molecular modeling study of complexes with cruzain.

Jasinski, G., Salas-Sarduy, E., Vega, D., Fabian, L., Martini, M., Moglioni, A.
16-03-2022
Bioorg Med Chem
https://pubmed.ncbi.nlm.nih.gov/35334448

The development of cruzipain inhibitors represents one of the most attractive challenges in the search for drugs for the treatment of Chagas disease. A recombinant form of this enzyme, cruzain, has been crystallized with numerous inhibitors, excluding thiosemicarbazones. These compounds have been established as potent inhibitors of cruzain, although there is very little data in the literature of thiosemicarbazones tested on cruzipain. In this work, we present the results of the evaluation of eleven thiosemicarbazones on cruzipain, isolated from T. cruzi epimastigotes, six of them previously evaluated on cruzain. For these latter, we studied through computational methods, the mode of interaction with the active site of cruzain and the contribution of geometric parameters to the possible mechanism of action involved in the observed inhibition. Finally, from some geometric parameters analyzed on modeled TSC-cruzain complexes, a semi-quantitative relationship was established that could explain the inhibitory activity of thiosemicarbazones on cruzipain, the enzyme actually present in the parasite.

Estimating chagas disease prevalence and number of underdiagnosed, and undertreated individuals in Spain.

Navarro, M., Reguero, L., Subirà, C., Blázquez-Pérez, A., Requena-Méndez, A.
02-03-2022
Travel Med Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35245657

Background: Chagas disease constitutes a public health problem, and Spain is the non-endemic country with the highest burden of disease outside the Americas. It represents a model for non-endemic countries regarding health policies to control the disease. This study is aimed to generate estimates of the T.cruzi prevalence and the number of undetected and untreated individuals with the infection in Spain and to compare them with the actual number of cases reported by official sources. **Methods:** Using aggregate data collected from the literature and official sources (Spanish National Statistics Institute; Spanish Agency of Medicines and Medical Devices) from 2010 to 2018, this study estimates the number of Chagas disease cases, plus the underdiagnosis and undertreatment rates. **Results:** We estimated that 55,367 out of 2,602,285 migrants originally from endemic countries were living with Chagas disease in Spain in 2018, accounting for a prevalence of 2.1%. Only 1% of these cases(613/455,566) were children aged 14 years or less resulting in a prevalence of 0.1%. Bolivian migrants accounted for 53.9% of the total estimated cases. The index of underdiagnosis and undertreatment were heterogeneous across different Spanish autonomous regions, but the overall index of underdiagnosis was around 71%, and the overall index of undertreatment was 82.5% in patients aged 15 years or older, and 60% in children. **Conclusion:** The burden of Chagas disease in Spain is considerable. Index of underdiagnosis and undertreatment are high, particularly in women of childbearing age, but they have improved in children since the implementation of antenatal screening programmes.

Identification of a tachykinin receptor and its implication in carbohydrate and lipid homeostasis in Rhodnius prolixus, a chagas disease vector.

Haddad, A., Leyria, J., Lange, A.
26-02-2022
Gen Comp Endocrinol
https://pubmed.ncbi.nlm.nih.gov/35231487

Neuropeptides and their receptors are fundamentally important in regulating many physiological and behavioural processes in insects. In this work, we have identified, cloned, and sequenced the tachykinin receptor (Rhopr-TKR) from Rhodnius prolixus, a vector of Chagas disease. The receptor is a G protein-coupled receptor belonging to the Rhodopsin Family A. The total length of the open reading frame of the Rhopr-TKR transcript is 1110 bp, which translates into a receptor of 338 amino acids. Fluorescent in-situ RNA-hybridization (FISH) for the Rhopr-TKR transcript shows a signal in a group of six bilaterally paired neurons in the protocerebrum of the brain, localized in a similar region as the insulin producing cells. To examine the role of tachykinin signaling in lipid and carbohydrate homeostasis we used RNA interference. Downregulation of the Rhopr-TKR transcript led to a decrease in the size of blood meal consumed and a significant increase in circulating carbohydrate and lipid levels. Further investigation revealed a close relationship between

tachykinin and insulin signaling since the downregulation of the Rhopr-TKR transcript negatively affected the transcript expression for insulin-like peptide 1 (Rhopr-ILP1), insulin-like growth factor (Rhopr-IGF) and insulin receptor 1 (Rhopr-InR1) in both the central nervous system and fat body. Taken together, these findings suggest that tachykinin signaling regulates lipid and carbohydrate homeostasis via the insulin signaling pathway.

Transcription Dependent Loss of an Ectopically Expressed Variant Surface Glycoprotein during Antigenic Variation in Trypanosoma brucei.

McLaughlin, E., Rubio-Pena, K., Dujeancourt-Henry, A., Glover, L.
01-03-2022
mBio
https://doi.org/10.1128/mbio.03847-21

In the mammalian host, Trypanosoma brucei is coated in a single-variant surface glycoprotein (VSG) species. Stochastic switching of the expressed *VSG* allows the parasite to escape detection by the host immune system. DNA double-strand breaks (DSB) trigger VSG switching, and repair via gene conversion results in an antigenically distinct *VSG* being expressed from the single active bloodstream-form expression site (BES). The single active BES is marked by *VSG* exclusion 2 (VEX2) protein. Here, we have disrupted monoallelic *VSG* expression by stably expressing a second telomeric *VSG* from a ribosomal locus. We found that cells expressing two *VSGs* contained one VEX2 focus that was significantly larger in size than the wild-type cells; this therefore suggests the ectopic *VSG* is expressed from the same nuclear position as the active BES. Unexpectedly, we report that in the double *VSG*-expressing cells, the DNA sequence of the ectopic copy is lost following a DSB in the active BES, despite it being spatially separated in the genome. The loss of the ectopic *VSG* is dependent on active transcription and does not disrupt the number or variety of templates used to repair a BES DSB and elicit a VSG switch. We propose that there are stringent mechanisms within the cell to reinforce monoallelic expression during antigenic variation. IMPORTANCE The single-cell parasite Trypanosoma brucei causes the fatal disease human African trypanosomiasis and is able to colonize the blood, fat, skin, and central nervous system. Trypanosomes survive in the mammalian host owing to a dense protective protein coat that consists of a single-variant surface glycoprotein species. Stochastic switching of one VSG for an immunologically distinct one enables the parasite to escape recognition by the host immune system. We have disrupted monoallelic antigen expression by expressing a second *VSG* and report that following DSB-triggered VSG switching, the DNA sequence of the ectopic *VSG* is lost in a transcription-dependent manner. We propose that there are strict requirements to ensure that only one variant antigen is expressed following a VSG switch, which has important implications for understanding how the parasite survives in the mammalian host.

New in morphometry: Geometric morphometry of the external female genitalia of Triatominae (Hemiptera: Reduviidae).

Belintani, T., de Paiva, V., de Oliveira, J., da Rosa, J.
19-02-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35192796

The study of geometric morphometry has an impact on Triatominae studies. Currently, several taxonomic and systematic studies use this approach. The Triatominae subfamily comprises three fossil species and 154 extant species potentially capable of transmitting Trypanosoma cruzi, the causative agent of Chagas disease. This study aims to evaluate the external female genitalia of adult triatomines using multivariate geometric morphometric approaches, not only for validation but also for systematic inferences. Specimens belonging to the genera Panstrongylus, Psammolestes, Rhodnius, and Triatoma were evaluated, in addition to two species previously included in Triatoma: T. longipennis and T. phyllosoma. The results show that the external female genitalia have operational morphology and allow characterization of the species and the genera of the Triatominae. In addition, the multivariate technique enabled delimitation of the phylogenetic relationships of the subfamily, presenting results consistent with systematic studies. It can be concluded that the external female genitalia evaluated by geometric morphometry is a useful character for the taxonomy and systematics of Triatominae.

Molecular data confirm Triatoma pallidipennis Stål, 1872 (Hemiptera: Reduviidae: Triatominae) as a novel cryptic species complex.

Cruz, D., Arellano, E.
19-02-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35189124

Triatoma pallidipennis constitues one of the most important Chagas disease vector in Mexico. Previous studies based on molecular data suggest T. pallidipennis as a complex of cryptic species. For that reason, we analyzed the phylogenetic relationships of T. pallidipennis using DNA sequences from the mitochondrial ND4 gene and the ITS-2 gene. In addition, the divergence times were estimated, and possible new taxa were delimited with three species delimitation methods. Finally, genetic distances and possible connectivity routes based on shared haplotypes were obtained among the T. pallidipennis populations. Five haplogroups (possible cryptic species) were found, based on delimitation methods and genetic distances. Haplogroup divergence began about 3 Ma, in the Pleistocene. Moreover, none of the haplogroups showed potential connectivity routes between them, evidencing lack of gene flow. Our results suggest the existence of a new cryptic species complex within what is currently recognized as a T.

pallidipennis.

Nanoconjugates based on a novel organic-inorganic hybrid silsesquioxane and gold nanoparticles as hemocompatible nanomaterials for promising biosensing applications.

Lima, D., Ribicki, A., Gonçalves, L., Hacke, A., Lopes, L., Pereira, R., Wohnrath, K., Fujiwara, S., Pessôa, C.
22-01-2022
Colloids Surf B Biointerfaces
https://pubmed.ncbi.nlm.nih.gov/35158220

A new hybrid organic-inorganic silsesquioxane material, 3-n-propyl(2-amino-4-methyl)pyridium chloride (SiAMPy$^+$Cl$^-$), was synthesized and successfully applied for the synthesis of stable nanoconjugates with gold nanoparticles (AuNPs-SiAMPy$^+$). SiAMPy$^+$Cl$^-$ was obtained through a simple sol-gel procedure by using chloropropyltrimetoxysilane and tetraethylorthosilicate as precursors and 2-amino-4-methylpyridine as the functionalizing agent. The resulting material was characterized by employing FTIR, XRD, and ^{1}H-, ^{13}C-, and ^{29}Si-NMR spectroscopy. The synthesis of AuNPs-SiAMPy$^+$ nanoconjugates was optimized through a 2^3 full factorial design. UV-VIS, FTIR, TEM, DLS, and ζ-potential measurements were used to characterize the nanoconjugates, which presented a spherical morphology with an average diameter of 5.8 nm. To investigate the existence of toxic effects of AuNPs-SiAMPy$^+$ on blood cells, which is essential for their future biomedical applications, toxicity assays on human erythrocytes and leukocytes were performed. Interestingly, no cytotoxic effects were observed for both types of cells. The nanoconjugates were further applied in the construction of electrochemical immunosensing devices, aiming the detection of anti-Trypanosoma cruzi antibodies in serum as biomarkers of Chagas disease. The AuNPs-SiAMPy$^+$ significantly enhanced the sensitivity of the biodevice, which was able to discriminate between anti-T. cruzi positive and negative serum samples. Thus, the AuNPs-SiAMPy$^+$-based biosensor showed great potential to be used as a new tool to perform fast and accurate diagnosis of Chagas disease. The promising findings described herein strongly confirm the remarkable potential of SiAMPy$^+$Cl$^-$ to obtain nanomaterials, which can present notable biomedical properties and applications.

Silent Trypanosoma evansi infection in humans from India revealed by serological and molecular surveys, and characterized by variable surface glycoprotein gene sequences.

Sengupta, P., Jacob, S., Chandu, A., Das, S.
12-02-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35157840

Background: The importance of emerging atypical human trypanosomosis is gaining momentum due to increasing detection and its possible impact on human health. A cross sectional study of atypical human trypanosomosis due to Trypanosoma evansi was carried out in Kolkata and Canning area of West Bengal state of India where previously a death was reported. Methods: In this study blood and serum samples from 173 individuals were collected during August to December 2014. To check the presence of antibodies against T. evansi, card agglutination test and for the presence of T. evansi specific DNA, PCR were conducted. Results: T. evansi infection was identified in 5.2% (9/173) human blood samples by CATT serological test (Card agglutination test for trypanosomosis). PCR targeting VSG gene sequences suggested active T. evansi infection in 2.89% (5/173). VSG gene sequences herein determined for five isolates from human cases shared high similarity (89.4-100%). Phylogenetic inference clustered the human isolates with other isolates from different host species from India and other countries, forming a clade exclusive of Indian isolates (84.0 to 100% sequence similarity). Conclusion: First report of symptomless human T. evansi infection detected by combined serological and PCR assays. First phylogenetic analysis of VSG gene sequences including human isolates of T. evansi in which Indian isolates of T. evansi from human and other hosts clustered in a single clade.

Trypanosoma cruzi infection in the wild Chagas disease vector, Mepraia spinolai: Parasitic load, discrete typing units, and blood meal sources.

Saavedra, M., Bacigalupo, A., Barrera, M., Vergara, M., Álvarez-Duhart, B., Muñoz-San Martín, C., Solís, R., Cattan, P.
10-02-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35150641

Background: Mepraia spinolai, a wild vector of Trypanosoma cruzi in Chile, is an abundant triatomine species that is frequently infected by the parasite that causes Chagas disease. The aim of this study was to determine if the parasitic load of T. cruzi in M. spinolai is related to its blood meal source and the infecting DTUs of T. cruzi. Methods: The vector was captured in rural areas. In the laboratory, DNA was extracted from its abdomen and T. cruzi was quantified using qPCR. Real time PCR assays for four T. cruzi DTUs were performed. Blood meal sources were identified by real-time PCR amplification of vertebrate cytochrome b gene sequences coupled with high resolution melting (HRM). Results: Trypanosoma cruzi was detected in 735 M. spinolai; in 484 we identified one blood meal source, corresponding to human, sylvatic, and domestic species. From these, in 224 we were able to discriminate the infecting DTU. When comparing the parasitic loads between the unique blood meal sources, no significant differences were found, but infections with more than one DTU showed higher parasitic loads than single infections. DTU TcI was detected in a high proportion of the samples. Conclusions: Higher parasitic loads are related to a greater number of T. cruzi DTUs infecting M. spinolai, and this triatomine seems to have a wide span of vertebrate species in its diet.

Assessment of a combined treatment with a therapeutic vaccine and benznidazole for the Trypanosoma cruzi chronic infection.

Prochetto, E., Bontempi, I., Rodeles, L., Cabrera, G., Vicco, M., Cacik, P., Pacini, M., Pérez Gianeselli, M., Pérez, A., Marcipar, I.
29-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35101415

The difficulties encountered in achieving treatments for chronic Chagas disease have promoted the investigation of new therapeutic strategies. In this study, we used two murine models of Trypanosoma cruzi chronic infection to determine the usefulness of applying a therapeutic vaccine alone or followed by benznidazole (Bz) chemotherapy. A vaccine formulation based on an N-terminal fragment of Trans-sialidase (TS) and Immunostimulant Particle Adjuvant (ISPA) - TSNt-ISPA was obtained. Firstly, the immunogenicity and protective capacity of TSNt-ISPA was demonstrated as a prophylactic formulation in an acute model of infection. Later, the formulation was assessed as a therapeutic vaccine alone or combined with (Bz) using two models of chronic infection. BALB/c mice chronically infected with Sylvio X10/4 or Tulahuen cl2 T. cruzi strains were not treated as control or treated only with the therapeutic vaccine TSNt-ISPA, with a combined treatment TSNt-ISPA+Bz (Bz applied after the vaccine), or only with Bz. The vaccination schedule consisted of TSNt-ISPA administration at days110, 120, and 130 post-infection (pi) and Bz administration was performed daily from day 140 to 170 pi. At day 273 pi, electrocardiographic (ECG) parameters, heart parasite load, myocarditis, and heart fibrosis were assessed. In both models, therapeutic administration of TSNt-ISPA reduced ECG alterations and the cardiac tissue damage observed in the chronic phase. Moreover, vaccine treatment significantly decreased heart parasite load in both Sylvio X10/4 and Tulahuen cl2 infected mice. The combined treatment, but not Bz or vaccine administration alone, allowed to restore ECG parameters in Tulahuen cl2 infected mice. The results indicate the usefulness of the therapeutic TSNt-ISPA formulation in BALB/c mice chronically infected with Sylvio X10/4 or Tulahuen cl2 strain. For the mice infected with T. cruzi Tulahuen cl2 strain, the combined treatment with the vaccine and Bz had a more positive effect on the course of heart disease than the individual treatments with the vaccine or Bz alone.

Impact of different protonation states on virtual screening performance against cruzain.

Santos, V., Campos, A., Waldner, B., Liedl, K., Ferreira, R.
05-01-2022
Chem Biol Drug Des
https://doi.org/10.1111/cbdd.14008

The cysteine protease cruzain is a Chagas disease target, exploited in computational studies. However, there is no consensus on the protonation states of the active site residues Cys25, His162, and Glu208 at the enzyme's active pH range. We evaluated the impact of different protonation states of these residues on docking calculations. Through a retrospective study with cruzain inhibitors and decoys, we compared the performance of virtual screening using four grids, varying protonation states of Cys25, His162, and Glu208. Based on enrichment factors and ROC plots, docking with the four grids affected compound ranking and the overall charge of top-ranking compounds. Different grids can be complementary and synergistic, increasing the odds of finding different ligands with diverse chemical properties.

LEISHMANIOSE

Transport mechanism of hydroxy-propyl-beta-cyclodextrin modified solid lipid nanoparticles across human epithelial cells for the oral absorption of antileishmanial drugs.

Parvez, S., Karole, A., Mudavath, S.
29-04-2022
Biochim Biophys Acta Gen Subj
https://pubmed.ncbi.nlm.nih.gov/35500665

Background: In this study, the transport mechanism of fluorescently labeled hydroxypropyl beta-cyclodextrin (HPβ-CD) modified SLNs loaded with Amphotericin B (AmB) and Paromomycin (PM) have been investigated by using in vitro human epithelial cell model of a human colonic adenocarcinoma cell line (Caco-2). Methods: Fabrication of HPβ-CD modified fluorescently labeled AmB and PM-loaded SLNs (HPβ-CD-FITC-DDSLNs) was performed by using the emulsion solvent evaporation method. Caco-2 cells were used to investigate different endocytosis and exocytosis pathways to be followed by the nanoparticles. Intracellular co-localization of nanoformulation with different organelles was investigated. Results: The toxicity studies have shown the biocompatible nature of the modified lipid nanoparticles. The average particle size and PDI of HPβ-CD-FITC-DDSLNs were found to be 187 ± 2.3 nm and 0.31 respectively. The most prevalent endocytosis mechanisms were shown to be macropinocytosis and caveolae (lipid raft) dependent pathways. The Golgi complex and endoplasmic reticulum are the confirmed destinations of HPβ-CD-FITC-DDSLNs in the Caco-2 cell monolayer, even though lysosomes have been shown to escape and play a minimal role during nanoparticle transport. Conclusion: HPβ-CD-FITC-DDSLNs were found to be biocompatible and safe for delivering hydrophobic as well as hydrophilic drugs through an oral route to target the RES system for the treatment of visceral leishmania. General significance: Understanding the process underlying the transport of modified solid lipid nanoparticles for oral drug delivery could be useful for many medicines with low solubility, permeability, and stability.

Dipeptidylcarboxypeptidase of Leishmania donovani: A potential vaccine molecule against experimental visceral leishmaniasis.

Balodi, D., Anand, A., Ramalingam, K., Yadav, S., Goyal, N.
26-04-2022
Cell Immunol
https://pubmed.ncbi.nlm.nih.gov/35500334

Visceral leishmaniasis is one of the deadliest parasitic diseases in the world. In the absence of an efficient and cost-effective drugs, development of an effective vaccine is the need of the day. In spite of several efforts, a successful vaccine against the disease has been elusive. We have evaluated immunoprophylactic efficacy of recombinant dipeptidycarboxypeptidase (rLdDCP), predominantly expressed in amastigotes, in chronic hamster model. rLdDCP induced in vitro lymphoproliferation and NO production in cured hamsters. Immunization with rLdDCP alone, or with BCG, caused significant reduction in parasite load suggesting strong protective response. The molecule also augmented the CMI response as depicted by an increased lymphocyte proliferation, NO production, DTH responses and increased levels of IgG2 in immunized hamsters. The vaccinated hamsters exhibited a surge in IFN-γ, TNF-α, IL-12 and iNOS levels but down-regulation of IL-10 and IL-4. Thus, the results suggest the potentiality of the rLdDCP as a strong candidate vaccine.

Therapeutic effect of *Prosopis strombulifera* (LAM) BENTH aqueous extract on a murine model of cutaneous leishmaniasis.

Lozano, E., Germanó, M., Troncoso, M., García Bustos, M., Luques, C., Cargnelutti, D.
16-08-2021
J Tradit Complement Med
https://doi.org/10.1016/j.jtcme.2021.08.009

Background and aim: *Prosopis strombulifera* (Lam.) Benth is a rhizomatous shrub native from different zones of Argentine Republic. *P. strombulifera* aqueous extract (PsAE) has different effects and several biological activities have been reported. The goal of this study was to analyze the activity of PsAE on a murine model of cutaneous leishmaniasis caused by *Leishmania amazonensis*. Experimental procedure: PsAE was orally administered at 150 mg/animal/day on BALB/c mice infected in the right footpad (RFP) with 1×10^5 promastigotes of *L. amazonensis*. As a chemotherapeutic control of treatment, animals receive a commercial form of meglumine antimoniate (MA) (Glucantime®, Aventis, Paris, France). Results and conclusion: We observe that the size of RFP lesions of infected mice without treatment showed a grade of inflammation, ulceration and necrosis at the site of infection much greater than that observed with PsAE or MA treatment. Moreover, PsAE was capable of decreasing parasite burden and splenic index. Furthermore, PsAE treated mice showed a significant decrease in O.D. of total anti-*Leishmania* IgG antibody responses against *L. amazonensis*. This decrease was similar to those observed when the reference drug, MA, was used. This would indicate that PsAE treatment inhibits or delays disease progression in mice. In conclusion, our findings suggest that PsAE could be a potential candidate to be used, as a new therapeutic strategy, to treat cutaneous leishmaniasis caused by *L. amazonensis*.

Etiological spectrum of persistent fever in the tropics and predictors of ubiquitous infections: a prospective four-country study with pooled analysis.

Bottieau, E., Van Duffel, L., El Safi, S., Koirala, K., Khanal, B., Rijal, S., Bhattarai, N., Phe, T., Lim, K., Mukendi, D., Kalo, J., Lutumba, P., Barbé, B., Jacobs, J., Van Esbroeck, M., Foqué, N., Tsoumanis, A., Parola, P., Yansouni, C., Boelaert, M., Verdonck, K., Chappuis, F.
02-05-2022
BMC Med
https://doi.org/10.1186/s12916-022-02347-8

Background: Persistent fever, defined as fever lasting for 7 days or more at first medical evaluation, has been hardly investigated as a separate clinical entity in the tropics. This study aimed at exploring the frequencies and diagnostic predictors of the ubiquitous priority (i.e., severe and treatable) infections causing persistent fever in the tropics. Methods: In six different health settings across four countries in Africa and Asia (Sudan, Democratic Republic of Congo [DRC], Nepal, and Cambodia), consecutive patients aged 5 years or older with persistent fever were prospectively recruited from January 2013 to October 2014. Participants underwent a reference diagnostic workup targeting a pre-established list of 12 epidemiologically relevant priority infections (i.e., malaria, tuberculosis, HIV, enteric fever, leptospirosis, rickettsiosis, brucellosis, melioidosis, relapsing fever, visceral leishmaniasis, human African trypanosomiasis, amebic liver abscess). The likelihood ratios (LRs) of clinical and basic laboratory features were determined by pooling all cases of each identified ubiquitous infection (i.e., found in all countries). In addition, we assessed the diagnostic accuracy of five antibody-based rapid diagnostic tests (RDTs): Typhidot Rapid IgM, Test-it™ Typhoid IgM Lateral Flow Assay, and SD Bioline Salmonella typhi IgG/IgM for Salmonella Typhi infection, and Test-it™ Leptospira IgM Lateral Flow Assay and SD Bioline Leptospira IgG/IgM for leptospirosis. Results: A total of 1922 patients (median age: 35 years; female: 51%) were enrolled (Sudan, n=667; DRC, n=300; Nepal, n=577; Cambodia, n=378). Ubiquitous priority infections were diagnosed in 452 (23.5%) participants and included malaria 8.0% (n=154), tuberculosis 6.7% (n=129), leptospirosis 4.0% (n=77), rickettsiosis 2.3% (n=44), enteric fever 1.8% (n=34), and new HIV diagnosis 0.7% (n=14). The other priority infections were limited to one or two countries. The only features with a positive LR≥3 were diarrhea for enteric fever and elevated alanine aminotransferase level for enteric fever and rickettsiosis. Sensitivities ranged from 29 to 67% for the three RDTs targeting S. Typhi and were 9% and 16% for the two RDTs targeting leptospirosis. Specificities ranged from 86 to 99% for S. Typhi detecting RDTs and were 96% and 97% for leptospirosis RDTs. Conclusions: Leptospirosis, rickettsiosis, and enteric fever accounted each for a substantial proportion of the persistent fever caseload across all tropical areas, in

addition to malaria, tuberculosis, and HIV. Very few discriminative features were however identified, and RDTs for leptospirosis and Salmonella Typhi infection performed poorly. Improved field diagnostics are urgently needed for these challenging infections. NCT01766830 at ClinicalTrials.gov.

Leishmania infantum infection rate in dogs housed in open-admission shelters is higher than of domiciled dogs in an endemic area of canine visceral leishmaniasis. Epidemiological implications.

Estevam, L., Veloso, L., Silva, G., Mori, C., Franco, P., Lima, A., Ássimos, G., Reis, I., Andrade-Filho, J., Araújo, M., Ribeiro, V., Almeida, A., Paz, G.
28-04-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35490730

Canine visceral leishmaniasis (CVL) is caused by Leishmania infantum and is endemic in many areas of southeastern Brazil. We have hypothesized that the prevalence of infection by L. infantum in dogs housed in open-admission animal shelters is beyond the range of 3.4 - 9.6% reported among dogs domiciled in similar CVL-endemic areas. Hence, this study aimed to determine the rate of L. infantum infection among dogs maintained in shelters and to investigate the epidemiology of CVL in such environments by analyzing hematological and biochemical parameters. A total of 627 dogs from 17 different shelters across the State of Minas Gerais were screened using the Dual-Path Platform test and enzyme-linked immunosorbent assay and 211 (33.6%) were found to be seropositive in both tests. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was performed on skin, bone marrow and lymphoid tissues of 118 seropositive dogs with inconclusive CVL clinical diagnosis and, of these, 78 (66.1%) were PCR+ for L. infantum and 7 (5.9%) were PCR+ for L. amazonensis. One dog presented a PCR-RFLP profile that was consistent with co-infection by both parasites. Leishmania amazonensis DNA was detected in skin samples of six single-infected dogs and this constitutes a novel finding. Dogs infected only with L. amazonensis were less debilitated than those infected by L. infantum, which showed typical clinical manifestations of CVL. The co-infected dog showed only mild clinical signs. The results presented herein not only support our original hypothesis but also suggest that dogs are potential reservoirs of L. amazonensis. Public health authorities should acknowledge their responsibility towards animals in collective shelters, recognize that they are potential foci of zoonotic diseases, and establish proper functioning directives to minimize transmission to humans and to other dogs.

Fifty years of struggle to control cutaneous leishmaniasis in the highest endemic county in Iran: A longitudinal observation inferred with interrupted time series model.

Aflatoonian, M., Sharifi, I., Aflatoonian, B., Salarkia, E., Khosravi, A., Tavakoli Oliaee, R., Bamorovat, M., Aghaei Afshar, A., Babaei, Z., Sharifi, F., Taheri Soodejani, M., Shirzadi, M., Gouya, M., Nadim, A., Sharifi, H.
29-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010271

Negligible data are available following major social activities and environmental changes on leishmaniasis. Therefore, how interactions between these events influence cutaneous leishmaniasis (CL) risk is not well-known. This longitudinal study was undertaken to explore the impact of interventions conducted between 1971 and 2020 in Bam county, which has had the highest disease burden in Iran. Only confirmed CL cases during this period were taken into account. Data were analyzed by SPSS 22 using the X2 test to assess the significance of the difference between proportions. Moreover, we used interrupted time series (ITS) to assess the impact of three environmental events during this period. Overall, 40,164 cases of CL occurred in the past five decades. Multiple complex factors were among the leading causes that synergistically induced the emergence/re-emergence of CL outbreaks in Bam. The main factors attributed negatively to CL control were cessation of malaria spraying activity, expansion of the city spaces, and a massive earthquake creating new breeding potentials for the vectors. The highest impact on CL incidence during these years was related to the earthquake [coefficient = 17.8 (95% CI: 11.3, 22.7); p-value < 0.001]. Many factors can contribute to CL outbreaks in endemic foci. They also can cause new foci in new areas. Since humans are the single reservoir for CL in this area, early detection and effective management significantly contribute to controlling CL to reduce the disease burden. However, essential evidence gaps remain, and new tools are crucial before the disease can ultimately be controlled. Nevertheless, sustained funding and more trained task forces are essential to strengthen surveillance and case management and monitor the interventions' impact.

Efficacy of imidacloprid/flumethrin collar in preventing canine leishmaniosis in Brazil.

Alves, G., de Oliveira, T., Rodas, L., Rozza, D., Nakamura, A., Ferrari, E., da Silva, D., Moraes Dos Santos, G., Calemes, E., Requena, K., Nagata, W., Santos-Doni, T., Bresciani, K.
27-04-2022
Transbound Emerg Dis
https://doi.org/10.1111/tbed.14571

The Leishmania infantum (synonym, Leishmania chagasi) causes life-threatening infection, namely canine leishmaniosis (CanL), which is a chronic zoonosis prevalent in various countries and spread by the bite of the infected Lutzomyia female sandfly in South America. The objective of the study was to assess the effectiveness of a polymer matrix collar containing made up of 10% imidacloprid and 4.5% flumetrin for the prevention of canine leishmaniosis from the hyperendemic region falling under Araçatuba municipality (Brazil). The research included a total of 146 dogs

chosen from 75 households. Test were initiaded via physical examination, weighing, and biological sample collection (blood, popliteal lymph node, and conjunctival swab) of these dogs was done in March 2018 (Day 0; GA, control = 69, GB, treated = 77) to initiate lab tests. Post-inclusion, the animals were monitored on the 120th, 240th, 360th, and 480th days, respectively. The usage of collars continued between 0 to 480 days before being substituted in second (D240) and fourth (D480) follow-up visits. On the whole, 25 dogs in GA (36.2 percent) and 3 in GB (3.9 percent) were found positive for L. infantum infection in a minimum of one diagnostic test used in the research. Therefore, the average collar effectiveness for protection from L. infantum infection was 89.2% ($p < 0.01$). In the last follow-up, the average incidence density rate for GA was 30.7%, whereas, for GB, it was 2.9%. The imidacloprid/flumethrin collars evaluated in the research were found to be safe and extremely efficient for the prevention of L. infantum infection through Lutzomyia species among the large population of dogs in highly prone endemic regions. This is a dependable and efficient technique aimed at reducing the occurrence and propagation of this illness among the population of canines, which would eventually reduce the human-health-related hazards. In Brazil, Lutzomyia spp. is a leading vector of the infection; thus, the collar can be used to limit infection in dogs and humans. The first trial was conducted in Brazil, including a 10% imidacloprid/4.5% flumethrin collar. In the initial assessment, the efficiency of the collar was 91.0% (D0 to D240). The effectiveness was 90.0% in the second assessment (D240 to D480). The mean effectiveness of the collar was 89.2% during the protection of dogs against L. infantum. The collar used for this evaluation was extremely useful and safe. This article is protected by copyright. All rights reserved.

3D Fib-sem structural insights into the architecture of sub-pellicular microtubules of trypanosoma cruzi epimastigotes.

Vidal, J., De Souza, W.
27-04-2022
Biol Cell
https://doi.org/10.1111/boc.202100038

Background information: Trypanosomatidae, which includes eukaryotic species agents of diseases like leishmaniasis, sleeping sickness and Chagas disease have special structures and organelles not found in mammalian cells. They present a layer of microtubules, known as subpellicular microtubules (SPMT), located underneath the plasma membrane and responsible for preserving cell morphology, cell polarity, the position of single copy organelles and morphological changes that occur throughout the protozoan life cycle. Even though a lot of knowledge about the SPMT is available, we still do not know exactly how each microtubule in the system is organized in three dimensions. Here, we use FIB-SEM to analyze the tridimensional organization of epimastigotes SPMT. Results: The high-resolution 3D analyses revealed that certain microtubules of the SPMT end more prematurely than the neighboring ones. Conclusions: These microtubules could (1) be shorter or (2) have the same length as the neighboring ones, assuming that those end up earlier at their other end, might be treadmilling/catastrophe events that have not yet been described in trypanosomatids. This article is protected by copyright. All rights reserved.

FRB domain of human TOR protein induces compromised proliferation and mitochondrial dysfunction in Leishmaniadonovani promastigotes.

Chakraborty, S., Mukherjee, S., Biswas, P., Ghosh, A., Siddhanta, A.
25-04-2022
Parasitol Int
https://pubmed.ncbi.nlm.nih.gov/35472440

Visceral leishmaniasis (VL) or Kala-azar, the second-largest parasitic killer worldwide, is caused by Leishmania donovani. The drugs to treat VL are toxic and expensive. Moreover, their indiscriminate use gave rise to resistant strains. The high rate of parasite proliferation within the host macrophage cells causes pathogenesis. In the proliferative pathway, FRB domain of TOR protein is ubiquitously essential. Although orthologues of mTOR protein are reported in trypanosomatids and Leishmania but therein depth molecular characterization is yet to be done. Considerable protein sequence homology exists between the TOR of kinetoplastidas and mammals. Interestingly, exogenous human FRB domain was shown to block G1 to S transition in mammalian cancer cells. Thus, we hypothesized that expression of human FRB domain would inhibit the proliferation of Leishmaniadonovani. Indeed, promastigotes stably expressing wild type human FRB domain show 4.7 and 1.5 folds less intra- and extra-cellular proliferations than that of untransfected controls. They also manifested 2.65 times lower rate of glucose stimulated oxygen consumption. The activities of all respiratory complexes were compromised in the hFRB expressing promastigotes. In these cells, depolarized mitochondria were 2-fold more than control cells. However, promastigotes expressing its mutant version (Trp^{2027}-Phe) has shown similar characteristics like untransfected cells. Thus, this study reveals greater insights on the conserved role of TOR in the regulation of the respiratory complexes in L. donovani. The slow growing variant of FRB expressing promastigotes will have great potential to be exploited as a prophylactic agent against leishmaniasis.

Large-scale survey for canine vector-borne parasites in free-ranging dogs and foxes from six diverse bioclimatic regions of Chile.

Sophia, D., Aitor, C., Claudia, U., Javier, C., Delia, G., Valeria, G., Ezequiel, H., Maria Stefania, L., Constanza, N., Irene, S., Nicole, S., Juliana, V., Gerardo, A., Domenico, V., Domenico, O., Javier, M.
24-03-2022
Vet Parasitol Reg Stud Reports
https://pubmed.ncbi.nlm.nih.gov/35431077

Chile is a large country with a marked range of climate

conditions that make it an ideal scenario for the study of vector-borne parasites (VBPs); however, knowledge about their distribution is limited to a few confined areas of this country. The presence of Hepatozoon spp., piroplasmids, Leishmania spp. and filarioids was investigated through molecular and serological methods in blood and serum samples of 764 free-ranging rural dogs, 154 Andean foxes (Lycalopex culpaeus), and 91 South American grey foxes (Lycalopex griseus) from six bioclimatic regions across Chile. Hepatozoon spp. DNA was exclusively detected in foxes (43% prevalence), including sequences closely related to Hepatozoon felis (24.1%; only Andean foxes), Hepatozoon americanum (16.2%; only grey foxes), and Hepatozoon canis (1.25%; in one grey fox). Risk factor assessment identified a higher probability of Hepatozoon infection in juvenile foxes. DNA of piroplasmids was detected in 0.7% of dogs (Babesia vogeli) but in no fox, whilst antibodies against Babesia sp. were detected in 24% of the dogs and 25% of the foxes, suggesting a wider circulation of canine piroplasmids than previously believed. A positive association between the presence of antibodies against Babesia and high Rhipicephalus sanguineus sensu lato burden was observed in dogs. Leishmania spp. DNA and antibodies were detected in 0.8% and 4.4% of the dogs, respectively. Acanthocheilonema reconditum was the only blood nematode detected (1.5% of the dogs and no fox). Differences in prevalence among bioregions were observed for some of the VBPs. These results expand our knowledge about the occurrence of vector-borne parasites in Chile, some of which are firstly reported herein. This information will facilitate the diagnosis of vector-borne diseases in domestic dogs and improve the control measures for both domestic and wild canids.

Tissue Specific Dual RNA-Seq Defines Host-Parasite Interplay in Murine Visceral Leishmaniasis Caused by Leishmania donovani and Leishmania infantum.

Forrester, S., Goundry, A., Dias, B., Leal-Calvo, T., Moraes, M., Kaye, P., Mottram, J., Lima, A.
06-04-2022
Microbiol Spectr
https://doi.org/10.1128/spectrum.00679-22

Visceral leishmaniasis is associated with hepato-splenomegaly and altered immune and hematological parameters in both preclinical animal models and humans. We studied mouse experimental visceral leishmaniasis caused by Leishmania infantum and Leishmania donovani in BALB/c mice using dual RNA-seq to investigate the transcriptional response of host and parasite in liver and spleen. We identified only 4 species-specific parasite expressed genes (SSPEGs; log2FC >1, FDR <0.05) in the infected spleen, and none in the infected liver. For the host transcriptome, we found 789 differentially expressed genes (DEGs; log2FC >1, FDR <0.05) in the spleen that were common to both infections, with IFNγ signaling and complement and coagulation cascade pathways highly enriched, and an additional 286 and 186 DEGs that were selective to L. donovani and L. infantum infection, respectively. Among those, there were network interactions between genes of amino acid metabolism and PPAR signaling in L. donovani infection and increased IL1β and positive regulation of fatty acid transport in L. infantum infection, although no pathway enrichment was observed. In the liver, there were 1,939 DEGs in mice infected with either L. infantum or L. donovani in comparison to uninfected mice, and the most enriched pathways were IFNγ signaling, neutrophil mediated immunity, complement and coagulation, cytokine-chemokine responses, and hemostasis. Additionally, 221 DEGs were selective in L. donovani and 429 DEGs in L. infantum infections. These data show that the host response for these two visceral leishmaniasis infection models is broadly similar, and ~10% of host DEGs vary in infections with either parasite species. IMPORTANCE Visceral leishmaniasis (VL) is caused by two species of *Leishmania* parasites, L. donovani in the Old World and L. infantum in the New World and countries bordering the Mediterranean. Although cardinal features such as hepato-splenomegaly and alterations in blood and immune function are evident, clinical presentation may vary by geography, with for example severe bleeding often associated with VL in Brazil. Although animal models of both L. donovani and L. infantum have been widely used to study disease pathogenesis, a direct side-by-side comparison of how these parasites species impact the infected host and/or how they might respond to the stresses of mammalian infection has not been previously reported. Identifying common and distinct pathways to pathogenesis will be important to ensure that new therapeutic or prophylactic approaches will be applicable across all forms of VL.

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

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

Background: The thymus is necessary for the differentiation of T cells, a process that is regulated by the type of antigens found in thymocytes, the environment of surrounding cells and the thymus architecture. There is evidence that infectious diseases may result in morphological changes in this organ, such as premature atrophy and decreased thymocyte proliferation, that can affect the immune response. Objectives: We characterised the morphology and tissue distribution of haematopoietic and stromal cells in the thymuses of dogs naturally infected with Leishmania infantum, with the aim to determine the changes that may contribute to the pathophysiology of the disease. Methods: Thymus samples were collected from 15 animals (aged 6 months to 5 years) ELISA-positive for leishmaniasis and from 10 dogs from non-endemic regions for leishmaniasis whose death was not related to infectious causes. The samples were submitted to histological processing and staining with Haematoxylin-Eosin to assess thymic morphometry and histopathological changes. Masson's trichrome staining was used to quantify the connective tissue present (collagen). The

immunohistochemical method was used to determine the cellular constitution of the thymus, using antibodies that aimed at marking T lymphocytes (anti-CD3), B lymphocytes (anti-CD79a), macrophages (anti- MAC387), mesenchymal cells (anti-vimentin), epithelial cells (anti-cytokeratin), cells in mitosis (anti-Ki67) and cells in apoptosis (anti-caspase-3). **Results:** The histopathological evaluation of infected dogs showed more signs consistent with thymus atrophy, including decreased parenchyma, infiltration of adipose and connective tissue near the capsule and between the lobules, lymphoid rarefaction mainly in the cortical region and loss of the cortical-medullary demarcation. In addition, we observed a decrease in the amounts of CD3 + T lymphocytes, macrophages (MAC387) and Ki67-positive cells and an increase in the number of cells positive for cytokeratin and CD79a (B lymphocytes). Finally, the parasite was detected in 46% of infected thymuses and may contribute for the observed changes. **Conclusions:** Apparently, leishmaniasis, like other infectious diseases, causes atrophy of the thymus and depletion of thymocytes with a relative increase in thymus epithelial cells. These morphological changes in the normal organisation of the thymus by mechanisms not yet well known may result in the abnormal release of T cells, with consequent damage to the host's immune response.

The knowns and unknowns of the efficacy of neem oil (Azadirachta indica) used as a preventative measure against Leishmania sand fly vectors (Phlebotomus genus).

Revue de littérature

Zatelli, A., Fondati, A., Maroli, M., Canine Leishmaniosis Working Group
19-03-2022
Prev Vet Med
https://pubmed.ncbi.nlm.nih.gov/35349879

Since domestic dogs are the main reservoir hosts of Leishmania infantum throughout the world, they are the main focus in terms of controlling zoonotic visceral leishmaniosis. To protect dogs from leishmaniosis, chemical repellents of durable efficacy are available in the form of collars, spot-on and sprays. However, the negative effects of chemical pesticides on the environment are well established as they affect animals and plants. This phenomenon has created the need for safer and more environmentally friendly substitutes. Plant extract-based insecticides and/or repellents have therefore been increasingly used by pet owners and veterinarians. Several botanical products have been tested as insecticides and/or repellents against a variety of bloodsucking arthropods that transmit human diseases. Among the products tested against Leishmania vectors, neem oil containing azadirachtin is the most studied. This study reviews the scientific literature concerning the efficacy of neem oil (azadirachtin-based products) against phlebotomine sand fly bites. A questionnaire was also administered to assess Italian veterinarians' attitudes to the use of neem oil. The survey was anonymous and consisted of three closed-ended questions. According to the data reported in the literature, the efficacy of neem oil in reducing the risk of sand fly bites has been tested against Phlebotomus papatasi, Phlebotomus perniciosus, Phlebotomus argentipes, Phlebotomus orientalis and Phlebotomus bergeroti. The efficacy of the products tested was expressed in percentages, ranging from 74.9% to 100%. The protection time was only available for six out of eight studies, ranging from "only during the first hour" (minimum protection time) to "all night" (expected maximum protection time). As regards the attitude to recommending the use of neem oil, 208 veterinarians participated in the online survey. Of the 126 veterinarians who recommended natural products, 119 (94.44%) reported that they recommended the use of neem oil-based products. Considering the limited data on the duration of protection and the dose of the active ingredient, more studies are required on the efficacy of neem oil-based products in reducing the risk of contracting canine leishmaniosis. These studies should also refer specifically to the concentration of the active ingredient as well as the interval of administration. Until such results are available, the use of azadirachtin-based products as the only topical products for the prevention of leishmaniosis in dogs is not recommended.

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

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

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

the use of rGTP/Sap. In conclusion, our preliminary data suggest that rGTP could be considered for further development as a vaccine candidate to protect against VL.

Antiproliferative properties of Turmerone on Leishmania major: Modes of action confirmed by antioxidative and immunomodulatory roles.

Mohseni, F., Sharifi, I., Oliaee, R., Babaei, Z., Mostafavi, M., Almani, P., Keyhani, A., Salarkia, E., Sharifi, F., Nave, H., Bamorovat, M., Alahdin, S., Sarlak, M., Tavakoly, R.
17-03-2022
Comp Immunol Microbiol Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35325685

Treatment of leishmaniasis by conventional synthetic compounds has faced a serious challenge worldwide. This study was performed to evaluate the effect and modes of action of aromatic Turmerone on the Leishmania major intra-macrophage amastigotes, the causative agent of zoonotic cutaneous leishmaniasis in the Old World. In the findings, the mean numbers of L. major amastigotes in macrophages were significantly decreased in exposure to Turmerone plus meglumine antimoniate (Glucantime®; MA) than MA alone, especially at 50 µg/mL. In addition, Turmerone demonstrated no cytotoxicity as the selectivity index (SI) was 21.1; while it induced significant apoptosis in a dose-dependent manner on L. major promastigotes. In silico molecular docking analyses indicated an affinity of Turmerone to IL-12, with the MolDock score of - 96.8 kcal/mol; which may explain the increased levels of Th1 cytokines and decreased level of IL-10. The main mechanism of action is more likely associated with stimulating a powerful antioxidant and promoting the immunomodulatory roles in the killing of the target organism.

Geographic distribution of *Meriones shawi,Psammomys obesus,* and *Phlebotomus papatasi the main reservoirs and principal vector* of zoonotic cutaneous leishmaniasis in the Middle East and North Africa.

Karmaoui, A., Ben Salem, A., Sereno, D., El Jaafari, S., Hajji, L.
04-03-2022
Parasite Epidemiol Control
https://doi.org/10.1016/j.parepi.2022.e00247

Rodents play a significant role in the balance of a terrestrial ecosystem; they are considered prey for many predators like owls and snakes. However, they present a high risk to agriculture (damaging crops) and health. These rodents are the main reservoirs of some vector-borne diseases like leishmaniasis. *Meriones shawi* (MS) and *Psammomys obesus* (PO) are the primary Zoonotic cutaneous leishmaniasis (ZCL) reservoirs in the Middle East and North Africa (MENA). A review on the MS and PO at the MENA scale was explored. A database of about 1500 papers was used. 38 sites were investigated as foci for MS and 36 sites for PO, and 83 sites of Phlebotomus papatasi (Pp) in the studied region. An updated map at the regional scale and the trend of the reservoir distribution was carried out using a performing proper density analysis. In this paper, climatic conditions and habitat characteristics of these two reservoirs were reviewed. The association of rodent density with some climatic variables is another aspect explored in a case study from Tunisia in the period 2009-2015 using Pearson correlation. Lastly, the protection and control measures of the reservoir were analyzed. The high concentration of the MS, PO, and Pp can be used as an indicator to identify the high-risk area of leishmaniasis infection.

Targeting chalcone binding sites in living Leishmania using a reversible fluorogenic benzochalcone probe.

Batista, A., Oliveira, S., Pomel, S., Commere, P., Mazan, V., Lee, M., Loiseau, P., Rossi-Bergmann, B., Prina, E., Duval, R.
14-03-2022
Biomed Pharmacother
https://pubmed.ncbi.nlm.nih.gov/35299122

Chalcones (1,3-diphenyl-2-propen-1-ones) either natural or synthetic have a plethora of biological properties including antileishmanial activities, but their development as drugs is hampered by their largely unknown mechanisms of action. We demonstrate herein that our previously described benzochalcone fluorogenic probe (HAB) could be imaged by fluorescence microscopy in live Leishmania amazonensis promastigotes where it targeted the parasite acidocalcisomes, lysosomes and the mitochondrion. As in the live zebrafish model, HAB formed yellow-emitting fluorescent complexes when associated with biological targets in Leishmania. Further, we used HAB as a reversible probe to study the binding of a portfolio of diverse chalcones and analogues in live promastigotes, using a combination of competitive flow cytometry analysis and cell microscopy. This pharmacological evaluation suggested that the binding of HAB in promastigotes was representative of chalcone pharmacology in Leishmania, with certain exogenous chalcones exhibiting competitive inhibition (ca. 20-30%) towards HAB whereas non-chalconic inhibitors showed weak capacity (ca. 3-5%) to block the probe intracellular binding. However, this methodology was restricted by the strong toxicity of several competing chalcones at high concentration, in conjunction with the limited sensitivity of the HAB fluorophore. This advocates for further optimization of this undirect target detection strategy using pharmacophore-derived reversible fluorescent probes.

The expression of PD-1 and its ligands increases in Leishmania infection and its blockade reduces the parasite burden.

Revue de littérature

Jafarzadeh, A., Kumar, S., Bodhale, N., Jafarzadeh, S., Nemati, M., Sharifi, I., Sarkar, A., Saha, B.
08-03-2022
Cytokine
https://pubmed.ncbi.nlm.nih.gov/35276636

The expression of programmed cell death protein-1 (PD-1) and its ligands- PD-L1 and PD-L2- on T cells and macrophages', respectively, increases in Leishmania infection. The PD-1/PD-L1 interaction induces T cell anergy, T cell apoptosis and exhaustion, diversion of T cells toward T_H2 and T-reg cells but inhibits M1 macrophage activities by suppression of nitric oxide (NO) and reactive oxygen species (ROS) production. These changes exacerbate Leishmania infection. As PD-L1-deficient, but not PD-L2-deficient, mice were protected againstL. mexicanainfection, differential roles have been proposed for PD-L1 and PD-L2 in mouse models of leishmaniasis. Blockade of PD-1/PD-L1 interaction in various in vitro and Leishmania-infected mouse, hamster and dog models enhanced IFN-γ and NO production, reduced IL-10 and TGF-β generation, promoted T cell proliferation and reduced parasite burden. Therefore, PD-1/PD-L1 blockade is being considered as a potential therapeutic strategy to restore protective immunity during leishmaniasis, particularly, in drug-resistant cases.

Down regulation of IL-10 and TGF-β1 mRNA expression associated with reduced inflammatory process correlates with control of parasitism in the liver after treatingL. infantuminfected dogs with the LBMPL vaccine therapy.

Mendes Roatt, B., Mirelle de Oliveira Cardoso, J., Cristiane Fortes de Brito, R., Eduardo Soares Reis, L., José Lucas Moreira, G., Melo de Abreu Vieira, P., Marques de Souza, F., Geraldo de Lima, W., Dian de Oliveira Aguiar-Soares, R., Cordeiro Giunchetti, R., Barbosa Reis, A.

05-03-2022

Cytokine

https://pubmed.ncbi.nlm.nih.gov/35259630

The liver plays an important role in human and canine visceral leishmaniasis, then it is considered as target to understand the mechanisms involved in the parasite control and a parameter to assess therapeutic responses. In this sense, our study focuses on evaluating the major alterations in the liver by histological (morphometric parenchyma inflammation/semi-quantitative portal inflammation), immunohistochemical assays (parasitism), and qPCR (parasitism and cytokine gene expression) in Leishmania infantum naturally infected dogs and treated with LBMPL vaccine. Animals were divided in four groups: NI group (n = 5): uninfected and untreated dogs; INT group (n = 7): L. infantum-infected dogs and not treated; MPL group (n = 6): L. infantum-infected dogs that received only monophosphoryl lipid A adjuvant, and LBMPL group (n = 10): L. infantum-infected dogs that received treatment with the vaccine composed by L. braziliensis disrupted promastigotes associated with MPL adjuvant. Ninety days after the end of treatments, the dogs were euthanized, and the liver was collected for the proposed evaluations. Significantly lower portal inflammatory reactions, and lower parenchyma inflammation were observed in the LBMPL group compared to INT and MPL groups. iNOS mRNA expression was higher in LBMPL group and in contrast, IL-10 and TGF-β1 mRNA expression was lower in this group when compared to INT group. Immunohistochemical and qPCR analysis showed significant parasite load reduction in LBMPL group compared to INT and MPL animals. Our data suggest that in naturally Leishmania-infected dogs, LBMPL vaccine reduces the damage in the hepatic tissue, being able to attenuate the type 2 immune response. It could be associated with a marked reduction in the parasitism decreasing liver inflammation in treated dogs. Along with previously obtained data, our results suggest that LBMPL vaccine can significantly contribute to the therapy strategy for L. infantum infected dogs.

Low expression of hypoxia-inducible factor-1α and differential expression of immune mediators during experimental infection with Leishmania (Viannia) spp.

Alves Mota, C., Stéfanie Sara Lopes Lera-Nonose, D., Ávila Brustolin, A., Chiqueto Duarte, G., Carolina Mota Dos Santos, M., Valdrinez Campana Lonardoni, M., Gomes Verzignassi Silveira, T.

02-03-2022

Cytokine

https://pubmed.ncbi.nlm.nih.gov/35247649

Leishmania (Viannia) species are the major agents of cutaneous leishmaniasis (CL) in the Americas. Ulcerative stigmatizing skin lesions generally characterize CL. The microenvironment during Leishmania infection is rich in inflammatory cells and molecules, which contrasts with low oxygen levels. The hypoxia-inducible factor (HIF)-1α activates several genes in response to hypoxia and inflammatory reactions, but its role in the CL course is poorly understood. We investigated the expression pattern of the genes HIF-1α, arginase, inducible NO synthase (iNOS), interferon (IFN)-γ, interleukin (IL)-12, and IL-10 in skin lesions and lymph nodes of golden hamsters infected with L. braziliensis, L. lainsoni, and L. naiffi. The animals were infected and followed for 105 days, with paw volume measurements and photos taken weekly. Euthanasia was performed at 0, 15, 56, and 105 days post-infection. The parasite load of paw and lymph node tissues were measured through absolute quantification at real-time PCR (qPCR), and reverse transcription qPCR (RT-qPCR) was applied to demonstrate the relative mRNA expression of the target genes. Among groups, animals infected with L. braziliensis had the highest parasite load in paws and lymph nodes. HIF-1α mRNA was down-regulated during chronic Leishmania (Viannia) infection but demonstrated less inhibition in hamsters infected with L. lainsoni and L. naiffi. Arginase was the most detectable gene in animals infected by L. braziliensis; IFN-γ and IL-10 genes were the most detectable in L. lainsoni and L. naiffi-infected animals. HIF-1α gene transcription seemed to be down-modulated byL. (Viannia)infection and was less inhibited by L. lainsoni and L. naiffi when compared toL. braziliensis. Animals with L. lainsoni and L. naiffi showed better control of the disease. Further studies are necessary to evaluate the mechanism influencing HIF-1α expression and its role on CL protection; such research could elucidate potential use of HIF-1α as a therapeutic target.

A conceptual model for understanding the zoonotic cutaneous leishmaniasis transmission risk in the Moroccan pre-Saharan area.

Karmaoui, A., Sereno, D., Maia, C., Campino, L., El Jaafari, S., Taybi, A., Hajji, L.
10-02-2022
Parasite Epidemiol Control
https://doi.org/10.1016/j.parepi.2022.e00243

Leishmanioses are of public health concern in Morocco, mainly the Zoonotic Cutaneous Leishmaniasis (ZCL) endemic in the Moroccan pre-Saharian area. Transmission of this disease depends on eco-epidemiological and socio-economic conditions. Therefore, a multivariable approach is required to delineate the risk and intensity of transmission. This will help outline main disease risk factors and understand interactions between all underlying factors acting on disease transmission at a local and regional scale. In this context, we propose a new conceptual model, the Biophysical-Drivers-Response-Zoonotic Cutaneous Leishmaniasis (BDRZCL), adapted to the Pre-Saharian area. The proposed model highlights how the physical and human drivers affect the environment and human health. The incidence of ZCL is linked to human activity and biophysical changes or by their interactions. The human response added to risk drivers are the main components that influence the biophysical part. This model improves our understanding of the cause-effect interactions and helps decision-makers and stakeholders react appropriately.

Small molecules as kinetoplastid specific proteasome inhibitors for leishmaniasis: a patent review from 1998 to 2021.

Revue de littérature

Imran, M., Khan, S., Abida, ., Alshrari, A., Eltahir Mudawi, M., Alshammari, M., Harshan, A., Alshammari, N.
11-03-2022
Expert Opin Ther Pat
https://doi.org/10.1080/13543776.2022.2045948

Introduction: Leishmaniasis is a neglected tropical infectious disease. The available limited therapeutic options for leishmaniasis are inadequate due to their poor pharmacokinetic profile, resistance, toxicity, high cost, and compliance problems. This warrants identification of new targets for the development of safer and effective anti-*Leishmania* therapy. The kinetoplastid specific proteasome (KSP) is a novel validated target to develop drugs against leishmaniasis. Area covered: This review focuses on all the published patent applications and granted patents related to the studied small molecules as KSP inhibitors (KSPIs) against *Leishmania* from 1998 to 31 December 2021. Expert opinion: A little amount of work has been done on KSPIs, but the study results are quite encouraging. LXE408 and GSK3494245 are two KSPIs in different phases of clinical trials. Some other small molecules have also shown KSP inhibitory potential, but they are not in clinical trials. The KSPIs are promising next-generation orally active patient compliant drugs against kinetoplastid diseases, including leishmaniasis. However, the main challenge to discover the KSPIs will be the resistance development and their selectivity against the proteasome of eukaryotic cells.

The anti-Leishmania potential of bioactive compounds derived from naphthoquinones and their possible applications. A systematic review of animal studies.

Revue de littérature

Ramos-Milaré, Á., Oyama, J., Murase, L., Souza, J., Guedes, B., Lera-Nonose, D., Monich, M., Brustolin, A., Demarchi, I., Teixeira, J., Lonardoni, M.
22-02-2022
Parasitol Res
https://doi.org/10.1007/s00436-022-07455-1

Leishmaniasis affects millions of people worldwide, and available treatments have severe limitations. Natural and derivative products are significant sources of innovative therapeutic agents. Naphthoquinones are natural or synthetic chemical compounds with broad biological activity. This systematic review aimed to evaluate the potential anti-Leishmania activity of bioactive compounds derived from naphthoquinones in animal models. Conducted in accordance with PRISMA guidelines, two blocks of MeSH terms were assembled: group I, Leishmania OR Leishmaniasis; group II, Atovaquone OR Lapachol OR Beta lapachone OR Naphthoquinones. The search was performed on PubMed, Web of Science, SCOPUS, EMBASE, and Lilacs databases. Twenty-four articles were retrieved and submitted for quality assessment using the SYRCLE critical appraisal tool. The in vivo anti-Leishmania potential of naphthoquinones was evaluated in visceral and cutaneous leishmaniasis using several measurement parameters. Analyzed compounds varied in structure, association with reference drugs, and encapsulation using a drug delivery system. The study design, including treatment protocol, differed between studies. The findings of the studies in this systematic review indicate the anti-Leishmania potential of naphthoquinones in vivo, with different treatment regimens directed against different Leishmania species. The employed drug delivery systems improve the results concerning selectivity, distribution, and required therapeutic dose. The immunomodulatory action was shown to be beneficial to the host, favoring an adequate immune response against infection by Leishmania parasites since it favored Th_1 responses. All studies presented a moderate to high risk of bias. These findings suggest that more studies are needed to assess the overall effectiveness and safety of these treatments.

Biofunctionalized Chrysin-conjugated gold nanoparticles neutralize Leishmania parasites with high efficacy.

Raj, S., Sasidharan, S., Tripathi, T., Saudagar, P.
17-02-2022
Int J Biol Macromol
https://pubmed.ncbi.nlm.nih.gov/35183598

Current treatments for leishmaniasis involve various drugs, including miltefosine and amphotericin B, which are associated with several side effects and high costs. Long-term use of these drugs may lead to the development of resistance, thereby reducing their efficiency. Chrysin (CHY) is a well-known, non-toxic flavonoid with antioxidant, antiviral, anti-inflammatory, anti-cancer, hepatoprotective, and neuroprotective properties. Recently we have shown that CHY targets the MAP kinase 3 enzyme of Leishmania and neutralizes the parasite rapidly. However, CHY is associated with low bioavailability, poor absorption, and rapid excretion issues, limiting its usage. In this study, we developed and tested a novel CHY-gold nanoformulation with improved efficacy against the parasites. The reducing power of CHY was utilized to reduce and conjugate with gold nanoparticles. Gold nanoparticles, which are already known for their anti-leishmanial properties, along with conjugated CHY, exhibited a decreased parasite burden in mammalian macrophages. Our findings showed that this biofunctionalized nanoformulation could be used as a potential therapeutic tool against leishmaniasis.

Evaluation of five different rapid immunochromatographic tests for canine leishmaniosis in Spain.

Villanueva-Saz, S., Martínez, M., Ramirez, J., Herrera, G., Marteles, D., Servián, M., Verde, M., Giner, J., Lacasta, D., Ruíz, H., Yzuel, A., Fernández, A.
16-02-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35181302

Canine leishmaniosis is a vector-borne disease caused by Leishmania parasites. Serological methods are the most common tests used for the diagnosis. This study aimed to evaluate and compare different serological commercial immunochromatographic rapid tests available in Spain to detect anti-Leishmania canine antibodies. The immunochromatographic tests were evaluated in different groups of dogs (healthy seronegative dogs (n = 21), naturally-sick dogs with moderate anti-Leishmania antibodies (n = 39), naturally-sick dogs with high anti-Leishmania antibodies (n = 37), dogs with the serological result of other pathogens infection (n = 20) and exposed dogs (n = 33)) admitted to the Veterinary Teaching Hospital of the University of Zaragoza (Spain) according to the clinical information sent with the sample to the laboratory for diagnostic purposes. The serology status was also routinely recorded through an in-house enzyme-linked immunosorbent assay (ELISA) and an in-house indirect immunofluorescence test (IFAT). The qualitative commercial serological immunochromatographic tests used were: FASTest LEISH, Uranotest Leishmania, Uranotest Leishmania 2.0, Speed Leish K, Witness Leishmania, and DFV Test Leishmania. Performance measures analyzed for each test were: sensitivity, specificity, and area under the receiver-operating (ROC) curve. The maximum specificity (1.00) was attained for Uranotest Leishmania and DFT Test Leishmania, followed by FASTest LEISH (0.98), Uranotest Leishmania 2.0 (0.98), Speed Leish K (0.98), and Witness Leishmania (0.95). The maximum sensitivity was attained for FASTest LEISH (1.00), followed by Uranotest 2.0 (0.97), Speed Leish K (0.97), Uranotest (0.96), and the lowest results with Witness (0.84) and DFV Test (0.59). Regarding the ROC curve, the maximum value was attained with the FASTest LEISH (0.99), followed by Uranotest (0.98), Uranotest 2.0 (0.97), Speed Leish K (0.97), Witness (0.90), and the lowest result with DFV Test (0.79). Efforts in the field of diagnosis should focus on establishing a commercial immunochromatographic test with high sensitivity and specificity with a reasonable cost-benefit balance.

Utility of the combination of hederagenin glucoside saponins and chromane hydrazone in the topical treatment of canine cutaneous leishmaniasis. An observational study.

Piragauta, S., Higuita-Castro, J., Arbeláez, N., Restrepo, A., Archbold, R., Quiñones, W., Torres, F., Echeverri, F., Escobar, G., Vélez, I., Montoya, A., Robledo, S.
18-02-2022
Parasitol Res
https://doi.org/10.1007/s00436-022-07467-x

Canine cutaneous leishmaniasis (CCL) is an emerging zoonotic infection endemic in several countries of the world. Due to variable response to therapy and frequency of relapses, a more effective, safer, and inexpensive treatment is needed. Recently, it was reported that the hederagenin glucoside saponins (SS) and chromane-derived hydrazone (TC2) combined in a 1:1 ratio has high potential in antileishmanial therapy since both compounds alter the survival of Leishmania and the ability to infect adjacent macrophage. Not only the skin permeation and the absorption of an ointment containing 2% TC2 and 2% SS (w/w) was determined in this work, but also the acute dermal toxicity in both in vitro and in vivo assays. Last, the effectiveness and safety of the topical therapy with 2% TC2-2% SS ointment was evaluated in an observational study in dogs with diagnosis of cutaneous leishmaniasis (CL). Both TC2 and SS diffused through pig ear skin and traces of TC2 (but not SS) were detected in the stratum corneum of mice at 6-24 h. Neither TC2 nor SS was detected in plasma. The acute dermal toxicity was negative. Treatment with 2% TC2-2% SS ointment produced a complete long-term clinical cure in 56 dogs (24 females and 32 males) from the Orinoco and Amazonas regions in southeastern Colombia without adverse effects. All dogs have remained disease-free for the last 24 months. In conclusion, these results support the use of this topical therapy as a safer and new first-line local treatment of CCL that could help limit the spread of CL from dogs to humans.

Functionalized 1,2,3-triazolium salts as potential agents against visceral leishmaniasis.

das Chagas Almeida, A., Meinel, R., Leal, Y., Silva, T., Glanzmann, N., Mendonça, D., Perin, L., Cunha-Júnior, E., Coelho, E., Melo, R., da Silva, A., Coimbra, E.

16-02-2022
Parasitol Res
https://doi.org/10.1007/s00436-022-07431-9

Visceral leishmaniasis (VL) is the most severe clinical form of leishmaniasis, being fatal if untreated. In search of a more effective treatment for VL, one of the main strategies is the development and screening of new antileishmanial compounds. Here, we reported the synthesis of seven new acetyl functionalized 1,2,3-triazolium salts, together with four 1,2,3-triazole precursors, and investigated their effect against different strains of L. infantum from dogs and humans. The 1,2,3-triazolium salts exhibited better activity than the 1,2,3-triazole derivatives with IC_{50} range from 0.12 to 8.66 µM and, among them, compound 5 showed significant activity against promastigotes (IC_{50} from 4.55 to 5.28 µM) and intracellular amastigotes (IC_{50} from 5.36 to 7.92 µM), with the best selective index (SI~6-9) and reduced toxicity. Our findings, using biochemical and ultrastructural approaches, demonstrated that compound 5 targets the mitochondrion of L. infantum promastigotes, leading to the formation of reactive oxygen species (ROS), increase of the mitochondrial membrane potential, and mitochondrial alteration. Moreover, quantitative transmission electron microscopy (TEM) revealed that compound 5 induces the reduction of promastigote size and cytoplasmic vacuolization. Interestingly, the effect of compound 5 was not associated with apoptosis or necrosis of the parasites but, instead, seems to be mediated through a pathway involving autophagy, with a clear detection of autophagic vacuoles in the cytoplasm by using both a fluorescent marker and TEM. As for the in vivo studies, compound 5 showed activity in a mouse model of VL at 20 mg/kg, reducing the parasite load in both spleen and liver (59.80% and 26.88%, respectively). Finally, this compound did not induce hepatoxicity or nephrotoxicity and was able to normalize the altered biochemical parameters in the infected mice. Thus, our findings support the use of 1,2,3-triazolium salts as potential agents against visceral leishmaniasis.

Screening organic repellent compounds against Lutzomyia longipalpis (Diptera: Psychodidae) present in plant essential oils: Bioassay plus an in silico approach.

Mota, T., Silva, C., Conceição, M., Fraga, D., Brodskyn, C., Neto, M., Santana, I., Mesquita, P., Leite, F., Magalhães-Júnior, J.
12-02-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35167802

In the Americas, Lutzomyia longipalpis is the most relevant sand fly species for the transmission of visceral leishmaniasis. For its vector control in Brazil, insecticide spraying has not shown persistent reduction in disease prevalence while some sand fly populations are reported resistant to the insecticides used in spraying. The usage of repellents and personal protection behavior can reduce vector borne diseases prevalence. Therefore, the search for new repellent compounds is needed to use together with insecticide spraying, especially from natural sources to overcome the resistance developed by some sand fly populations to the compounds commercially used. In silico strategies have been applied together with repellency bioassays successfully identifying new bioactive compounds from natural sources. Thus, the present study aimed to screen repellent potential of neem (Azadirachta indica), citronella (Cymbopogon winterianus), bushy matgrass (Lippia alba) and 'alecrim do mato' (Lippia thymoides) essential oils against L. longipalpis and to identify potential repellent compounds by chemical analysis and in silico approach. Plant essential oils were extracted from leaves and repellency bioassays were performed on volunteers using colony reared L. longipalpis. Aside from neem oil, all other tested essential oil has shown a reduced number of sand fly bites using higher concentrations. Chemical composition from oils was assessed and its compounds were screened on a pharmacophore model using odorant binding protein 1 (OBP1). All essential oils were majorly composed of either oxygenated monoterpenes, except for the oil extracted from neem which was composed of sesquiterpene hydrocarbons. Molecular docking was performed with the compounds that best superimposed in the OBP1 pharmacophore model, identifying those binding to OBP4, which is associated with insect repellency behavior. Citronellol, Citronellol acetate, Citronellal and Geranyl acetate showed similar interactions with OBP4 binding site as DEET. Thus, it is suggested that these compounds are able to bind to L. longipalpis OBP4 generating repellent behavior in sand flies.

Knowledge, attitude and prevention measures of students towards cutaneous leishmaniasis in Delanta district, Northeast Ethiopia.

Dires, A., Kumar, P., Gedamu, S., Yimam, W., Ademe, S.
25-01-2022
Parasite Epidemiol Control
https://doi.org/10.1016/j.parepi.2022.e00241

Background and aims: Leishmaniasis is a neglected tropical disease which causes significant morbidity and mortality, particularly in developing countries. Cutaneous leishmaniasis (CL) is the main form of leishmaniasis that affects the skin. Knowledge and perception of people about leishmaniasis has a great impact to prevent the disease in endemic areas. Hence, the aim of this study was to assess the knowledge, attitude and preventive measures of Wegeltena secondary school students towards CL in Delanta district, one of the endemic areas in Northeast Ethiopia. **Methods:** A facility-based cross-sectional study was conducted from January 4 to 20, 2021 at Wegeltena secondary school in Delanta district, Northeast Ethiopia. A pre-tested, interviewer administered structured questionnaire was used to collect the data. Multivariable logistic regression analysis was utilized to measure the degree of association between outcome and independent variables. Statistically significant association with the outcome variables was declared at a *p*-value of <0.05. **Results:** A total of 388 students were participated in the study. In overall, 27.6% and 34.5% of participants had good knowledge and favorable attitude towards CL, respectively.

Being grade 12 (AOR = 2.56; 95% CI: 1.23-5.29) and dwelling in urban areas (AOR = 1.78; 95% CI: 1.09-2.89) were determinants of good knowledge. However, female sex (AOR = 1.96; 95% CI: 1.21-3.18) and had good knowledge about CL (AOR = 3.75; 95% CI: 2.26-6.21) were significantly associated with favorable attitude of respondents towards the disease. **Conclusion:** In this study, nearly three-fourth of participants had poor knowledge about CL and two-third of them had unfavorable attitude towards the disease. Level of education and residence were determinants of respondents' knowledge about CL. Moreover, sex and level of knowledge about CL were determinants of respondents' attitude towards the disease. Therefore, an intensified health education program shall be implemented in schools that are found in endemic areas.

Anti-leishmanial activity of *Avicennia marina* (*Avicenniaceae* family) leaves hydroalcoholic extract and its possible cellular mechanisms.

Rashno, Z., Sharifi, I., Oliaee, R., Tajbakhsh, S., Sharififar, F., Sharifi, F., Hatami, A., Faridi, A., Babaei, Z.
19-01-2022
Parasite Epidemiol Control
https://doi.org/10.1016/j.parepi.2022.e00239

Natural products are the main source of potent antioxidants and anti-leishmanial agents. This study was aimed to evaluate *Avicennia marina* (*Avicenniaceae* family) extract inhibitory effect against *Leishmania tropica* by accessing apoptotic markers and arginase activity. The *A. marina* were extracted and phytochemical analysis conducted. The inhibitory effect of *A. marina* was evaluated on *L. tropica* promastigote and amastigote forms, compared to meglumine antimoniate (Glucantime, MA) as standard drug. The level of apoptosis, Reactive Oxygen Species (ROS) production and arginase activity was assessed in *A. marina*-treated cells compared to control group. Phytochemical screening of *A. marina* extract showed strong presence of tannins and saponins. We demonstrated the inhibitory effect of *A. marina* on promastigote stages in a dose dependent manner. Also, lower 50% inhibitory concentration (IC_{50}) value of amastigotes was indicated in *A. marina* group compared with the standard group of Glucantime (60.57 ± 1.46 vs. 73.19 ± 10.12 μg/mL, respectively, $P < 0.05$). Besides, *A. marina* represented no cytotoxicity as the selectivity index (SI) was 10.7. Also, it showed the potential to induce early apoptosis of 46.5% in promastigotes at 125 μg/mL concentration. Significant reduction of arginase level was observed in both *A. marina*-treated cells and promastigotes. The promising results indicated higher effectiveness of *A. marina* in decreasing parasite growth, inducing apoptosis in promastigotes, increasing ROS production and decreasing arginase level. So, *A. marina* can be a native plant candidate for anti-leishmanial drug in tropical regions with cutaneous leishmaniasis due to *L. tropica*.

Molecular-based assay for genotyping *Leishmania* spp. from clinically suspected cutaneous leishmaniasis lesions in the Garmian area, Kurdistan Region of Iraq.

Tawfeeq, H., Ali, S.
24-01-2022
Parasite Epidemiol Control
https://doi.org/10.1016/j.parepi.2022.e00240

Cutaneous leishmaniasis (CL) is highly prevalent in southern Iraq and neighboring countries, but is non-endemic to the Kurdistan Region of Iraq, particularly in the Garmian area. This study aimed to investigate the causative agent of CL at the molecular level by amplifying the small subunit (18S) rRNA and internal transcribed spacer 1 (ITS1) region. The present study was conducted from December 2019 to December 2020 at Kalar General Hospital, Kalar, Kurdistan Region, Iraq. Eighty-five clinical specimens were collected selectively from patients with suspected CL lesions via fine needle aspiration. After parasitic genomic DNA was extracted from the removed fluid, PCR and DNA sequencing targeting the 18S rRNA and ITS1 region were performed for molecular detection and species identification. Additionally, for 14 samples, the target bands of amplified DNA fragments for both 18S rRNA and ITS1 were extracted and sequenced via Sanger method using both the directional primers employed in the PCR. Seventy-one (83.53%) of the 85 suspected patients had CL, based on amplification of 18S rRNA and ITS1 via PCR. The sequence analysis revealed that all samples were *Leishmania major*. Phylogenetic analysis based on ITS1 was also performed. Our study revealed that our molecular method was an efficient technique for detecting CL and a valuable method for identifying *Leishmania* species in clinical samples. Sequence analysis indicated that the causative agent of CL in the Garmian area was *L. major* and the disease was rural in origin.

In silico analysis of Leishmania proteomes and protein-protein interaction network: Prioritizing therapeutic targets and drugs for repurposing to treat leishmaniasis.

Prava, J., Pan, A.
05-02-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35134348

Leishmaniasis is a serious world health problem and its current therapies have several limitations demanding to develop novel therapeutics for this disease. The present study aims to prioritize novel broad-spectrum targets using proteomics and protein-protein interaction network (PPIN) data for 11 Leishmania species. Proteome comparison and host non-homology analysis resulted in 3605 pathogen-specific conserved core proteins. Gene ontology analysis indicated their involvement in major molecular functions like DNA binding, transportation, dioxygenase, and catalytic activity. PPIN analysis of these core proteins identified eight hub proteins (viz., vesicle-trafficking protein (LBRM2903_190011800), ribosomal proteins S17

(LBRM2903_34004790) and L2 (LBRM2903_080008100), eukaryotic translation initiation factor 3 (LBRM2903_350086700), replication factor A (LBRM2903_150008000), U3 small nucleolar RNA-associated protein (LBRM2903_340025600), exonuclease (LBRM2903_200021800), and mitochondrial RNA ligase (LBRM2903_200074100)). Among the hub proteins, six were classified as drug targets and two as vaccine candidates. Further, druggability analysis indicated three hub proteins, namely eukaryotic translation initiation factor 3, ribosomal proteins S17 and L2 as druggable. Their three-dimensional structures were modelled and docked with the identified ligands (2-methylthio-N6-isopentenyl-adenosine-5'-monophosphate, artenimol and omacetaxine mepesuccinate). These ligands could be experimentally validated (in vitro and in vivo) and repurposed for the development of novel antileishmanial agents.

Predictive modeling of sand fly distribution incriminated in the transmission of Leishmania (Viannia) braziliensis and the incidence of Cutaneous Leishmaniasis in the state of Paraná, Brazil.

Revue de littérature

de Almeida, T., Neto, I., Consalter, R., Brum, F., Rojas, E., da Costa-Ribeiro, M.
29-01-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35101414

Southern Brazil concentrates a considerable number of cases of cutaneous leishmaniasis reported since 1980, and Paraná is the state that most records CL cases in the region. The main sand fly species incriminated as vectors of Leishmania (Viannia) braziliensis (Vianna,1911) are Migonemyia (Migonemyia) migonei (França, 1920), Nyssomyia (Nyssomyia) neivai (Pinto, 1926) and Nyssomyia (Nyssomyia) whitmani (Antunes & Coutinho, 1936). In this study, we evaluated areas with climatic suitability for the distribution of these vectors and correlated these data with CL incidence in the state. The occurrence points of Mg. migonei, Ny. neivai, and Ny. whitmani were extracted from a literature review and field data. For CL analysis in the state of Paraná, data were obtained from the Informatics Department of the Unified Health System of Brazil (DATASUS), covering the period from 2001 to 2019. The layers of bioclimatic variables from the WorldClim database were used in the study. Species distribution modeling was developed using the MaxEnt Software version 3.4.4. ArcGIS software version 10.5 was used to develop suitability maps and the graphical representation of disease incidence. The AUC values were acceptable for all models (> 0,8). Bioclimatic variables BIO13 and BIO14 were the most influential in the distribution of Mg. migonei, while BIO19 and BIO6 were the variables that most influenced the distribution of Ny. neivai, and Ny. whitmani was most influenced by variables BIO5 and BIO9. During 19 years, 4992 cases of CL were reported in the state by 286 municipalities (71,6%). Northern Paraná showed the highest number of areas with very high and high climatic suitability for the occurrence of these species, coinciding with the highest number of CL cases. The modeling tools allowed analyzing the association between climatic variables and the geographical distribution of CL in the state. Moreover, they provided a better understanding of the climatic conditions related to the distribution of different species, favoring the monitoring of risk areas, the implementation of preventive measures, risk awareness, early and accurate diagnosis, and consequent timely treatment.

Cutaneous leishmaniasis over a tattoo mimicking keratoacanthoma in Southern Europe.

Prados-Carmona, Á., Gómez-Valcárcel, J., Velasco-Amador, J., Martin-Castro, A., Navarro-Triviño, F.
25-01-2022
J Eur Acad Dermatol Venereol
https://doi.org/10.1111/jdv.17930

Retrospective Study of Canine Peripheral Lymphadenopathy in a Mediterranean Region: 130 Cases.

Santiago, R., Feo, L., Pastor, J., Sanchez, M., Bercianos, A., Puig, J.
07-01-2022
Top Companion Anim Med
https://pubmed.ncbi.nlm.nih.gov/35007777

Lymphadenopathy is a common clinical concern in dogs. Causes of lymphadenopathy include neoplasia, infection, and immune-mediated diseases. Seasonal infectious diseases should be considered as a potential cause of lymphadenopathy in endemic regions, such as the Mediterranean region. Therefore, the purpose of this study was to evaluate the causes of peripheral lymph node enlargement in dogs in a Mediterranean region (north- eastern Spain). In addition, we aimed to assess the relationship between peripheral lymphadenopathy and other clinical data. Medical records of dogs admitted to 2 referral hospitals in Barcelona (Spain) with peripheral lymphadenopathy and cytological evaluation of lymph nodes, during a 4-year period (2015-2019) were included. One hundred and thirty dogs met the inclusion criteria. The most common final clinical diagnoses were lymphoproliferative neoplasia (36%) and dermatological disease (18.4%), followed by vector borne infectious disease (VBID; 16.5%). In the VBID group, 19 dogs were positive for Leishmania infantum and 2 dogs were positive for heartworm antigen. The presence of lymphadenopathy as the only clinical sign, generalized peripheral lymphadenopathy and internal lymphadenopathy was more frequent in dogs with lymphoma. The patients with metastatic neoplasms had significantly more localized lymphadenopathy compared to the other diagnosis groups. Twenty percent of the dogs had fever and this was more frequent in the immunemediated disease group. Our findings suggest that lymphoma is the most likely cause of lymphadenopathy in dogs. Clinicians should consider

lymphoproliferative neoplasia in dogs with general peripheral lymphadenopathy concurrent with internal (abdominal or thoracic) lymphadenopathy and without other clinical signs. A higher incidence of immune-mediated disease was found in the population of febrile dogs included in this study.

Unusual presentations of cutaneous leishmaniasis: pearls for correct diagnosis.

Mohaghegh, F., Hatami, P., Saber, M., Heidari, A., Zolfaghari, A., Rezaee, M., Aryanian, Z.
04-01-2022
Int J Dermatol
https://doi.org/10.1111/ijd.16035

In-silico studies on Myo inositol-1-phosphate synthase of *Leishmania donovani* in search of anti-leishmaniasis.

Sinha, M., Jagadeesan, R., Kumar, N., Saha, S., Kothandan, G., Kumar, D.
17-11-2020
J Biomol Struct Dyn
https://doi.org/10.1080/07391102.2020.1847194

Myo-inositol is one of the vital nutritional requirements for the *Leishmania* parasites' survival and virulence in the mammalian host. . Myo-inositol-1-phosphate synthase (MIPS) is responsible for the synthesis of myo-inositol in *Leishmania*, which plays a vital role in *Leishmania's* virulence to mammalian hosts. Earlier studies suggest MIP synthase as a potential drug target against which valproate was used as a drug. So, MIP synthase can be used as a target for anti-leishmanial drugs, and its inhibition may help in preventing leishmaniasis. The present study aims to identify valproate's potent analogs as drugs against MIP synthase of *L. donovani* (*Ld*-MIPS) with minimum side effects and toxicity to host.In this study, the three-dimensional structure of *Ld*-MIPS was built, followed by active site prediction. Ligand-based virtual screening was done using hybrid similarity recognition methods. The best 123 valproate analogs were filtered based on their quantitative structure activity relationship (QSAR) properties and were docked against *Ld*-MIPS using FlexX, PyRx and iGEMDOCK software. The topmost five ligands were selected for molecular dynamics simulation and pharmacokinetic analysis based on the docking score. Simulation studies up to 30ns revealed that all five lead molecules bound with *Ld*-MIPS throughout MD simulation and there was no variation in their backbone. All the chosen inhibitors exhibited good pharmacokinetics/ADMET predictions with an excellent absorption profile, metabolism, oral bioavailability, solubility, excretion, and minimal toxicity, suggesting that these inhibitors may further be developed as anti-leishmaniasis drugs to prevent the spread of leishmaniasis.Communicated by Ramaswamy H. Sarma.

CYSTICERCOSE

Quality of life in patients with symptomatic epilepsy due to neurocysticercosis.

Zapata, W., Yang, S., Bustos, J., Gonzales, I., Saavedra, H., Guzman, C., Pretell, E., Garcia, H., Cysticercosis Working Group In Peru
25-04-2022
Epilepsy Behav
https://pubmed.ncbi.nlm.nih.gov/35483205

Background: Neurocysticercosis (NCC) is a common cause of late-onset epilepsy worldwide, but there is still minimal information regarding its impact on a patient's quality of life. This study evaluated quality of life in a series of patients with epilepsy secondary to NCC using the QOLIE (Quality of Life in Epilepsy)-31 questionnaire. Methodology: This cross-sectional study included 155 Peruvian patients between 16 and 70 years of age with epilepsy due to viable intraparenchymal NCC, who enrolled in two trials of anti-parasitic treatment during the period 2006-2011. The QOLIE-31 questionnaire was applied before the onset of anti-parasitic treatment. The associations between QOLIE-31 scores, sociodemographic characteristics, clinical, and neuroimaging data were analyzed with Kruskal-Wallis test and generalized linear models (GLM). Results: The average QOLIE-31 score was 55.8 (SD ± 7.6), with 119 individuals (76.8%) scoring in the poor quality-of-life category. Generalized tonic-clonic seizures and secondarily generalized epileptic seizures were associated with a lower QOLIE-31, as well as a low level of education with a value of $p = 0.05$. There were no associations between QOLIE-31 scores and other variables such as sex, age, antiepileptic medication, number of parasitic cysts, and number of compromised brain regions. On multivariate analysis, a greater number of generalized epileptic seizures maintained a statistically significant association with detrimental QOLIE-31 scores. Conclusion: Quality of life is affected in NCC, mainly in relation to the number of prior generalized epileptic seizures.

Movements of free-range pigs in rural communities in Zambia: an explorative study towards future ring interventions for the control of Taenia solium.

Van Damme, I., Pray, I., Mwape, K., Trevisan, C., Coudenys, F., Mubanga, C., Mwelwa, C., Vaernewyck, V., Dorny, P., O'Neal, S., Gabriël, S.
27-04-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05264-0

Background: Taenia solium typically affects resource-poor communities where pigs are allowed to roam freely, and sanitation and hygiene levels are suboptimal. Sustainable, long-term strategies are urgently needed to control the disease. Geographically targeted interventions, i.e. screening or treatment of taeniosis among people living near infected pigs (defined as ring screening and ring treatment, respectively), have been shown to be effective control options in Peru. However, these results might not be directly

generalizable to sub-Saharan African settings. Pig movements play a vital role in the transmission and, consequently, the success of ring interventions against T. solium. The aim of the present study was to explore roaming patterns of pigs in T. solium endemic communities in Zambia as a first step toward evaluating whether ring interventions should be considered as a treatment option in Zambia. **Methods:** In total, 48 free-roaming pigs in two rural neighborhoods in the Eastern Province of Zambia were tracked using a Global Positioning System (GPS) receiver. Tracking took place in April (end of the rainy season) 2019 and October (end of the dry season) 2019. The number of revisitations and the time spent within rings of different radii (50, 100 and 250 m) around the coordinates of each pig owner's household were calculated for each pig. **Results:** The total tracking time for 43 pigs in the final analysis set ranged between 43 and 94 h. Pigs spent a median of 31% and 13% of the tracked time outside the 50- and 100-m radius, respectively, although large variations were observed between pigs. Overall, 25 pigs (58%) went outside the 250-m ring at least once, and individual excursions lasting up to 16 h were observed. In the dry season, 17 out of 23 pigs went outside the 250-m radius compared to only eight out of 20 pigs in the rainy season (P=0.014). **Conclusions:** In our study sites in Zambia, the majority of pigs spent most of their time within 50 or 100 m of their owner's home, and these results are comparable with those on Peruvian pigs. Both radii could therefore be considered reasonable options in future ring interventions.

Case 305.

Caruso, S., Marrone, G., Gentile, G.
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Radiology
https://doi.org/10.1148/radiol.210452

A 27-year-old man was admitted to the emergency department with fever and thoracic pain. In the previous 6 months, the patient lost a substantial amount of weight (12 kg). His family history was negative for cardiac disease. Electrocardiography revealed sinus rhythm, and diffuse T-wave inversion. Two-dimensional echocardiography was performed (Fig 1) and revealed normal left systolic function (ejection fraction, 60%). Laboratory tests showed elevated levels of high-sensitivity cardiac troponin (1.07 ng/mL; normal value, <0.015 ng/mL), high levels of C-reactive protein (16 mg/dL; normal range, 0-5 mg/dL), and leukocytosis with an eosinophilia level of 8710/μL (normal level, <400/μL). Parasitic and infectious diseases (*Toxocara canis*, strongyloides, filariasis, cysticercosis, fasciola, trichinella, echinococcosis) were excluded based on blood and fecal test results. Corticosteroid therapy was started, and the patient was dismissed. A few days later, he was readmitted to the emergency department with a headache and suddenly blurred vision. Neurologic and ophthalmologic findings were normal, and MRI of the brain was performed (Fig 2). Cardiac MRI (Fig 3) was performed 2 days later and revealed the following quantitative results: *(a)* left ventricular end-diastolic volume (LVDV) of 165 mL (LVDV/body surface area [BSA], 89 mL/m^2; normal range, 64-100 mL/m^2), left ventricular end-systolic volume (LVSV) of 80 mL (LVSV/BSA, 43 mL/m^2; normal range, 17-39 mL/m^2); stroke volume (SV) of 85 mL (SV/BSA, 46 mL/m^2; normal range, 43-67 mL/m^2); and ejection fraction of 52% and *(b)* right ventricular end-diastolic volume (RVDV) of 163 mL (RVDV/BSA, 88 mL/m^2; normal range, 63-111 mL/m^2), right ventricular end-systolic volume (RVSV) of 81 mL (RVSV/BSA, 44 mL/m^2; normal range, 32-92 mL/m^2); stroke volume (SV) of 82 mL (SV/BSA, 44 mL/m^2; normal range, 39-71 mL/m^2); and ejection fraction of 50%.

Prevalence and genetic variance of Taenia hydatigena in goats and sheep from northern Ghana: Preliminary data on a globally neglected livestock parasite.

Addy, F., Adu-Bonsu, G., Dickson, A., Dankwa, D., Aryee, R., Dufailu, O., Romig, T., Wassermann, M.
19-02-2022
Vet Parasitol Reg Stud Reports
https://pubmed.ncbi.nlm.nih.gov/35431069

Cysticercosis caused by the larval stages of Taenia hydatigena has a significant global impact on livestock production, particularly of goats and sheep. Despite this, global data on prevalence and genetic variance of this parasite are still scarce. In Ghana, as in most African countries, numerous anecdotal observations agree that it is widespread and frequent. To obtain baseline data, we screened 251 goats and 248 sheep in northern Ghana (Upper East Region) for T. hydatigena metacestode and molecularly characterized the isolates using the mtDNA cox1 gene sequence. Prevalence was 58.57% in goats and 60.48% in sheep, confirming the abundance of this parasite in the region. Gene sequences revealed high diversity (π 0.00346, hd 0.809) and significant negative Tajima D and Fu's Fs values, a characteristic of a population experiencing an expansion after a recent bottleneck. This is the first account of the genetic structure of T. hydatigena in Ghana, intended as a basis for subsequent studies in the region.

Epidemiological status of bovine cysticercosis and human taeniasis in Eastern Ethiopia.

Abera, A., Sibhat, B., Assefa, A.
02-04-2022
Parasite Epidemiol Control
https://doi.org/10.1016/j.parepi.2022.e00248

Bovine cysticercosis and human taeniasis are among the leading cause of economic loss in Ethiopia due to organ condemnation and treatment costs. A cross-sectional study was conducted from September 2017 to July 2018 on randomly selected carcasses from Jigjiga, Babile and Dire Dawa town municipal abattoirs to estimate the prevalence of bovine cysticercosis. Besides, a questionnaire was administered to the human population of these towns to understand risk of human taeniasis. The overall prevalence of *Cysticercus bovis* was 27.3% (302/1108). Among the examined

predilection sites, the highest prevalence was observed in the liver (9.6%), and the tongue (8.5%). From the total of 686*C. bovis* cysts collected, 289 (42.0%) were viable, while the other 397 (58.0%) were non-viable cysts. Three predictors, namely study location, age and body condition, were significantly associated with *C. bovis* ($p \leq 0.001$). Among the 900 respondents interviewed, 432 had contracted *Taenia saginata* infection. Risk factors like occupation, sex, marital status, educational status and raw beef consumption habit were significantly associated with *T. saginata* infection ($p \leq 0.001$). The findings of this study indicated the importance of bovine cysticercosis and taeniasis in the study areas. Therefore, attention should be given to public awareness and detailed meat inspection for the safety of the public and promotion of the country's meat industry.

Proliferative cells in racemose neurocysticercosis have an active MAPK signalling pathway and respond to metformin treatment.

Orrego, M., Verastegui, M., Vasquez, C., Garcia, H., Nash, T., Cysticercosis Working Group in Peru
17-02-2022
Int J Parasitol
https://pubmed.ncbi.nlm.nih.gov/35182540

Racemose neurocysticercosis is an aggressive infection caused by the aberrant expansion of the cyst form of Taenia solium within the subarachnoid spaces of the human brain and spinal cord, resulting in the displacement of the surrounding host tissue and chronic inflammation. We previously demonstrated that the continued growth of the racemose bladder wall is associated with the presence of mitotically active cells but the nature and control of these proliferative cells are not well understood. Here, we demonstrated by immunofluorescence that the racemose cyst has an active mitogen-activated protein kinases (MAPK) signalling pathway that is inhibited after treatment with metformin, which reduces racemose cell proliferation in vitro, and reduces parasite growth in the murine model of Taenia crassiceps cysticercosis. Our findings indicate the importance of insulin receptor-mediated activation of the MAPK signalling pathway in the proliferation and growth of the bladder wall of the racemose cyst and its susceptibility to metformin action. The antiproliferative action of metformin may provide a new therapeutic approach against racemose neurocysticercosis.

DRACUNCULOSE

Countries recommit to Guinea worm eradication by 2030.

Burki, T.
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Lancet Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35460659

ECHINOCOCCOSE

Echinococcosis in immunocompromised patients: A systematic review.

Ghasemirad, H., Bazargan, N., Shahesmaeili, A., Harandi, M.
28-04-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35490729

Background: Human echinococcoses are the infection caused by the larval stages of different species of the genus Echinococcus, mostly E. granulosus and E. multilocularis. There is no aggregated information on the nature and characteristics echinococcosis in patients with immunodeficiency. This study presents a systematic review of the current literature published on the status of echinococcosis in immunocompromised individuals. Methods: An electronic search of related articles in four major databases (PubMed, Scopus, Web of Science and Google Scholar) was performed up to November 2021. All related studies meeting the inclusion criteria were assessed for qualitative analysis. Data available on different characteristics of the diseases were extracted. The data were subsequently categorized into two subgroups: Cystic Echinococcosis (CE) and Alveolar Echinococcosis (AE). Results: Twenty-eight articles related to the existence of echinococcosis in immunocompromised hosts were included. HIV/AIDS was found as the most frequent condition in immunocompromised CE patients. Most of the CE cases with immunodeficiency were female (66.4%). The dominant stages of the cysts were CE2 and CE3. Surgery was performed for 76.2% of the patients. A high mortality rate of 23.8% was recorded in CE patients. Malignancies was the dominant condition in AE patients. Conclusion: Findings of the present study can potentially improve our understanding of the impact of immunodeficiency syndromes on echinococcoses and contribute to an improved diagnosis, treatment and quality of care in immunocompromised patients suffering from cystic and alveolar echinococcosis.

Identification of B-cell dominant epitopes in the recombinant protein P29 from Echinococcus granulosus.

Lv, Y., Li, S., Zhang, T., Zhu, Y., Tao, J., Yang, J., Chang, L., Wu, C., Zhao, W.
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Immun Inflamm Dis
https://doi.org/10.1002/iid3.611

Introduction: Echinococcus granulosus (E. granulosus) causes a hazardous zoonotic parasitic disease. This parasite can occupy the liver and several areas of the body, causing incurable damage. Our previous studies have provided evidence that the recombinant protein P29 (rEg.P29) exhibit immune protection in sheep and mice against pathological damage induced by E. granulosus, showing its potential as candidate for vaccine development. However, information on the B-cell epitopes of rEg.P29 has not yet been reported. Methods: Immunological

model was established in mice with rEg.P29. SDS-PAGE and Western blot were used to identify protein. Screening for B-cell dominant epitope peptides of rEg.P29 by enzyme-linked immunosorbent assay (ELISA) and immune serum. Dominant epitopes were validated using ELISA and flow cytometry. Multiple sequence alignment analysis was performed using BLAST and UniProt. **Results:** Immunization with rEg.P29 induced intense and persistent antibody responses, and the epitope of the dominant antigen of B cells are identified as rEg.P29$_{166-185}$ (LKNAKTAEQKAKWEAEVRKD). Anti-rEg.P29$_{166-185}$ -specific antibodies lack epitopes against IgA, IgE, and IgG3, compared to anti-rEg.P29-specific antibodies. However, anti-rEg.P29$_{166-185}$ IgG showed comparatively higher titers, as determined among those peptides by endpoint titration. In addition, rEg.P29 and rEg.P29$_{166-185}$ promote B-cell activation and proliferation in vitro. The dominant epitopes are relatively conserved in different subtypes of the rEg.P29 sequence. **Conclusion:** rEg.P29$_{166-185}$ can act as a dominant B-cell epitope for rEg.P29 and promote cell activation and proliferation in the same way as rEg.P29.

Towards delimitation of the Echinococcus multilocularis parasite's southernmost range in France.

Umhang, G., Richomme, C., Caillot, C., Bastid, V., Boucher, J., Moyen, J., Novella, C., Richoux, B., Davoust, B., Boué, F.
24-03-2022
Vet Parasitol Reg Stud Reports
https://pubmed.ncbi.nlm.nih.gov/35431062

Alveolar echinococcosis is a severe, potentially fatal, parasitic disease caused by ingestion of microscopic eggs of Echinococcus multilocularis. The lifecycle of the parasite is essentially sylvatic, and based on a prey-predator relationship between red foxes and small rodents. A westward expansion from the eastern historical focus has been reported in France, though the parasite has also been detected in the southern Alps. While the focus in the Auvergne region (central France) was described in the 1980s, the southern delimitation of the actual endemic area, especially in the south, was unknown in the absence of dedicated surveys. Red fox samples were collected from 2013 to 2020 in the framework of other transversal epidemiological studies in five sampling areas from southwestern and southeastern France. One hundred and seven intestines were analysed by SSCT, and 221 faecal samples from intestines were analysed by copro-qPCR. None of the 328 foxes exhibited E. multilocularis worms or DNA. Although the presence of E. multilocularis cannot be totally excluded in the departments from the study areas, the sample size tested argues for an absence of the parasite in these studied areas, which is in accordance with the currently known endemic situation in France. These new data are helpful in determining the southernmost limit of E. multilocularis distribution in France. The warm, dry Mediterranean climate in the southeastern areas is less favourable to the transmission of E. multilocularis and especially to the survival of eggs in the environment than the climate in the French Alps or Liguria (Italy) climate where the parasite is present. The intermediate area between the southwestern study areas and the historical focus of Auvergne, which is separated by around 150 km, will be investigated in the coming years. Moreover, an ongoing national surveillance programme on E. multilocularis in foxes is targeting French departements along the edge of the known endemic area both in the southeast and southwest. The data produced will supplement the results of this study, thus greatly helping to define the current distribution of E. multilocularis in France and to target prevention measures to reduce human exposure.

A review of human alveolar echinococcosis in the Republic of Armenia from 2008 to 2020.

Revue de littérature

Manukyan, A., Avetisyan, L., Sahakyan, G., Jimenez, A., Paronyan, L., Gevorgyan, K., Vanyan, A.
26-02-2022
Parasite Epidemiol Control
https://doi.org/10.1016/j.parepi.2022.e00246

Background: Since the 90s' *Echinococcus multilocularis* infection has expanded the geographical area and central-eastern European countries had seen first alveolar echinococcosis (AE) human cases. AE is considered to be a very rare disease in Europe with average incidences of 0.03-0.2/100,000 inhabitants/year. Because of a suitable orography, this study aims to confirm whether there are human AE cases in Armenia, identify areas at risk, and also estimate AE annual incidence. **Methods:** Retrospective AE case finding was carried out at main multi-profile medical centers equipped with the modern diagnostic means. The medical records of all patients with liver surgery admitted between January 2008 and June 2020 were reviewed. A specific form was developed in EpiInfo v.7.2. Annual national incidence was estimated using population denominators provided by the National Institute of Statistics. **Results:** Overall, 11 AE cases have been identified. All patients were diagnosed at advanced stages, with subsequent poor prognosis and costly treatment. Confirmation was based on tissue biopsy and medical i$maging results. Age ranged from 12 to 58 years with a median of 33 yrs. Patients were from rural communities, mostly in the Gegharkunik region (6 cases, 55%). Annual average incidence of AE was 0.033/100,000 varying between 0.032 in 2008 and 0.1 in 2017. **Conclusions:** There are human AE cases happening in Armenia since more a decade ago. In the absence of an AE surveillance system, the burden of AE disease is difficult to estimate. Development of national AE guidelines with a case definition should help enforcing registry of all cases, early diagnosis and also clinical and public awareness.

Molecular characterization of the serotonergic transporter from the cestode Echinococcus granulosus: pharmacology and potential role in the nervous system.

Camicia, F., Vaca, H., Guarnaschelli, I., Koziol, U., Mortensen, O.,

Fontana, A.
16-02-2022
Parasitol Res
https://doi.org/10.1007/s00436-022-07466-y

Echinococcus granulosus, the etiological agent of human cystic echinococcosis (formerly known as hydatid disease), represents a serious worldwide public health problem with limited treatment options. The essential role played by the neuromuscular system in parasite survival and the relevance of serotonin (5-HT) in parasite movement and development make the serotonergic system an attractive source of drug targets. In this study, we cloned and sequenced a cDNA coding for the serotonin transporter from E. granulosus (EgSERT). Bioinformatic analyses suggest that EgSERT has twelve transmembrane domains with highly conserved ligand and ionic binding sites but a less conserved allosteric site compared with the human orthologue (HsSERT). Modeling studies also suggest a good degree of conservation of the overall structure compared with HsSERT. Functional and pharmacological studies performed on the cloned EgSERT confirm that this protein is indeed a serotonin transporter. EgSERT is specific for 5-HT and does not transport other neurotransmitters. Typical monoamine transport inhibitors also displayed inhibitory activities towards EgSERT, but with lower affinity than for the human SERT (HsSERT), suggesting a high divergence of the cestode transporter compared with HsSERT. In situ hybridization studies performed in the larval protoscolex stage suggest that EgSERT is located in discrete regions that are compatible with the major ganglia of the serotonergic nervous system. The pharmacological properties, the amino acidic substitutions at important functional regions compared with the HsSERT, and the putative role of EgSERT in the nervous system suggest that it could be an important target for pharmacological intervention.

Determination of macrophage types by immunohistochemical methods in the local immune response to liver hydatid cysts in sheep.

Atmaca, H.
09-02-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35149039

Cystic echinococcosis is a zoonotic parasitic disease caused by Echinococcus granulosus. The main hosts in the life cycle of this parasite are dogs and other carnivores; The intermediate hosts are human, sheep, goat, cattle, pig, buffalo, horse and camel. The parasite damages the tissue by forming lesions in the form of fluid-filled cysts in the liver. These lesions are bounded by a layer of local inflammatory cells formed by the host. In the layer formed by this inflammatory response, there are lymphocytes, neutrophils and eosinophil leukocytes, including macrophages. Samples taken from sheep with hydatid cysts in their livers were followed for pathological analysis, and then histopathological and immunohistochemical examinations were performed. After histopathological examinations, the types of macrophages involved in the local immune response against cysts in the liver were determined by immunohistochemical methods using anti-INOS and anti-IL-10 antibodies. INOS and IL-10 immunopositivity were detected in all samples. Statistically, no significant difference was observed between these immunopositivity. This showed that both macrophage types are involved in the local immune response to hydatid cyst, and that Th1 and Th2 immune response stimulation continues together. It was concluded that in future studies that will be planned and experimentally, it will be possible to reveal more clearly how these macrophage types take part in the local immune response.

Pulmonary Echinococcus in children: A descriptive study in a LMIC.

Mfingwana, L., Goussard, P., van Wyk, L., Morrison, J., Gie, A., Mohammed, R., Janson, J., Wagenaar, R., Ismail, Z., Schubert, P.
14-02-2022
Pediatr Pulmonol
https://doi.org/10.1002/ppul.25854

Background: Echinococcus granulosus is a major public health problem in lower middle-income countries (LMIC). Children are commonly diagnosed with cysts in the lungs and/or the liver. Objectives: The purpose of this study was to describe a pediatric cohort diagnosed with pulmonary Cystic Echinococcus (CE) and treated with a combination of medical and surgical therapy. Methods: This was a retrospective study performed between July 2017 and December 2020 at Tygerberg Hospital, South Africa. Clinical, laboratory, radiological, medical, and surgery-related outcomes were reviewed. Results: The cohort consisted of 35 children, 17 (49%) were male, with a mean age of 9±5.4 years. The most frequently encountered presenting symptom was cough (93%) followed by fever (70%). Isolated pulmonary CE accounted for the majority of cases (74%) with left lower lobe predominance. A significant proportion of the cohort exhibited chest computed tomography (CT) characteristics consistent with complicated pulmonary CE. Eighteen (58%) children had a positive indirect hemagglutination assay (IHA) test result. All children received medical treatment whilst 30 (86%) of children required surgery. Children with complicated pulmonary CE stayed a mean of 12.5±6.6 days, while those with simple cysts stayed 6.8±1.5 days. Conclusion: Isolated pulmonary CE is common in children, whereas extrapulmonary cysts are uncommon. Pulmonary CE is diagnosed using chest X-ray and, CT imaging. IHA serology has limited diagnostic utility for pulmonary CE. Combined surgery and chemotherapy remains the gold standard for treating pulmonary CE.

A giant renal hydatid cyst with pleural extension and epiploic localization management: A case report.

Trigui, M., Ayed, K., Triki, W., Abbassi, I., Baraket, O., Bouchoucha, S.
20-01-2022
Urol Case Rep
https://doi.org/10.1016/j.eucr.2022.102005

Hydatidosis is a rare parasitic disease that is endemic in many countries of the Mediterranean basin caused by the larval form of Echinococcus Granulosus. Among unusual localizations, renal involvement is rare, especially extension to the pleural cavity. Herein, we report a rare case of 75-year-old woman with giant renal hydatid cyst complicated by pleural extension. The patient was successfully treated with a median phreno-laparotomy.The renal hydatid cyst was completely emptied with resection of the epiploic hydatid cyst.The diaphragmatic breach was closed after resection of the necrotic margins. With 1 month albendazole therapy.

Liver and lung hydatid cysts with transdiaphragmatic rupture treated by radical surgery.

Rodríguez-Laiz, G., Melgar, P., Bolufer, S., Navarro Martínez, J., Ramia, J.
21-12-2021
Ann R Coll Surg Engl
https://doi.org/10.1308/rcsann.2021.0183

Hydatidosis is a parasitic disease caused by *Echinococcus granulosus*, a tapeworm that is endemic in certain parts of the world. We present a case of hepatopulmonary hydatidosis with diaphragm involvement and close contact with the suprahepatic inferior vena cava treated with radical surgery. We discuss therapeutical surgical options (approach and type of surgery).

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

Case 305.

Caruso, S., Marrone, G., Gentile, G.
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Radiology
https://doi.org/10.1148/radiol.210452

A 27-year-old man was admitted to the emergency department with fever and thoracic pain. In the previous 6 months, the patient lost a substantial amount of weight (12 kg). His family history was negative for cardiac disease. Electrocardiography revealed sinus rhythm, and diffuse T-wave inversion. Two-dimensional echocardiography was performed (Fig 1) and revealed normal left systolic function (ejection fraction, 60%). Laboratory tests showed elevated levels of high-sensitivity cardiac troponin (1.07 ng/mL; normal value, <0.015 ng/mL), high levels of C-reactive protein (16 mg/dL; normal range, 0-5 mg/dL), and leukocytosis with an eosinophilia level of 8710/µL (normal level, <400/µL). Parasitic and infectious diseases (*Toxocara canis*, strongyloides, filariasis, cysticercosis, fasciola, trichinella, echinococcosis) were excluded based on blood and fecal test results. Corticosteroid therapy was started, and the patient was dismissed. A few days later, he was readmitted to the emergency department with a headache and suddenly blurred vision. Neurologic and ophthalmologic findings were normal, and MRI of the brain was performed (Fig 2). Cardiac MRI (Fig 3) was performed 2 days later and revealed the following quantitative results: *(a)* left ventricular end-diastolic volume (LVDV) of 165 mL (LVDV/body surface area [BSA], 89 mL/m^2; normal range, 64-100 mL/m^2), left ventricular end-systolic volume (LVSV) of 80 mL (LVSV/BSA, 43 mL/m^2; normal range, 17-39 mL/m^2); stroke volume (SV) of 85 mL (SV/BSA, 46 mL/m^2; normal range, 43-67 mL/m^2); and ejection fraction of 52% and *(b)* right ventricular end-diastolic volume (RVDV) of 163 mL (RVDV/BSA, 88 mL/m^2; normal range, 63-111 mL/m^2), right ventricular end-systolic volume (RVSV) of 81 mL (RVSV/BSA, 44 mL/m^2; normal range, 32-92 mL/m^2); stroke volume (SV) of 82 mL (SV/BSA, 44 mL/m^2; normal range, 39-71 mL/m^2); and ejection fraction of 50%.

Molecular identification of cercaria Fasciola gigantica in lymnaeid snails in Kulon Progo, Yogyakarta.

Prastowo, J., Priyowidodo, D., Sahara, A., Nurcahyo, W., Nugraheni, Y., Awaludin, A.
16-02-2022
Vet Parasitol Reg Stud Reports
https://pubmed.ncbi.nlm.nih.gov/35431065

Lymnaeid snails play an essential role in transmitting fasciolosis as intermediate hosts. Therefore, this study aims to use the molecular method to identify liver fluke in lymnaeid snails. A total of 320 lymnaeid snails were collected from a rice field. The samples were dissected to collect cercaria and identified using polymerase chain reaction. Furthermore, the internal transcribed spacer 2 (ITS2) was used as the target gene to identify the species of cercaria. The result showed that 3.75% (12/320) of the snails were infected by Fasciola gigantica, while the phylogenetic tree based on ITS2 showed that the cercaria in this study was monophyletic and similar to species from several countries in Southeast Asia, including China. Furthermore, the haplotype network showed that all four cercaria samples were similar with sequences from several countries. This study suggests that the F. gigantica cercaria isolated from lymnaeid snails in Kulon Progo, Yogyakarta, Indonesia, has a sequence similar to that of other species in Southeast Asian countries, although no hybrid type was detected in these sequences. This is the first report on the molecular identification of cercaria F. gigantica isolated from lymnaeid snails in Yogyakarta, Indonesia.

Paragonimiasis diagnosed by CT-guided transthoracic lung biopsy: Literature review and case report.

Cong, C., Anh, T., Ly, T., Duc, N.

14-03-2022
Radiol Case Rep
https://doi.org/10.1016/j.radcr.2022.02.046

More than 40 different species of the parasitic flatworm *Paragonimus* have been identified worldwide, including in Vietnam, but only 10 species are known to cause disease in humans, particularly *Paragonimus westermani. Paragonimus* are transmitted through the ingestion of raw foods, especially freshwater shrimp, and crab. Paragonimiasis causes pneumonia, which can present as acute or chronic, with symptoms including prolonged cough, chest pain, shortness of breath, and hemoptysis. Hematologic changes include eosinophilia and the presence of specific antibodies for *Paragonimus* in the blood. Diagnosis is confirmed when *Paragonimus* specimens or eggs are found in the sputum or pleural fluid. The specificity of imaging is not high, but imaging can be used to guide the diagnosis. After the failure of microbiological diagnostic methods, lung biopsy can be used to confirm a diagnosis of paragonimiasis. We present a paragonimiasis case associated with unique features, including epidemiologic factors, atypical clinical signs, no increases in blood eosinophils, and negative microbiological tests. Although the patient was suspected of tuberculosis or lung cancer, imaging studies were consistent with the presence of lung flukes. Three transthoracic lung biopsies were performed, and pathology revealed a cystic structure containing *Paragonimus* on the third biopsy.

Insights to helminth infections in food and companion animals in Bangladesh: Occurrence and risk profiling.

Nath, T., Eom, K., Choe, S., Islam, S., Sabuj, S., Saha, E., Tuhin, R., Ndosi, B., Kang, Y., Kim, S., Bia, M., Park, H., Lee, D.
22-02-2022
Parasite Epidemiol Control
https://doi.org/10.1016/j.parepi.2022.e00245

Introduction: A better understanding of the epidemiology of helminths in animal hosts is important in order to ensure animal welfare, public health and food safety. The aim of this study was to explore parasitism in common animals in Bangladesh. Perception and understanding of animal owners regarding parasitic diseases management were also assessed. Materials and methods: A total of 550 fecal samples were examined from common animals (cattle, goat, pig, chicken, dog, and cat) across three different areas of Bangladesh (Dhaka, Sylhet, and Chattogram) from January 2020 to March 2021. Associated risk factors were assessed through questionnaire surveys among 50 animal owners. Parasitological assessment was done using the combined sedimentation-flotation method, and factors associated with infection were modeled using mixed-effects logistic regression. Results: Helminths including *Toxocara* sp., *Spirometra* sp., *Capillaria* sp., *Trichuris* sp., opisthorchiid, *Ascaris suum*, *Fasciola* sp., *Paramphistomum* sp., strongyles, hookworms, roundworms, taeniid, and acanthocephalans were detected in the examined animals, and overall prevalence was 59.3% (95% CI = 54.1-62.8). Parasites were found in 61.3% (245/400) of food animals and 54.0% (81/150) of companion animals. Animal owners have a good understanding of parasite infections; however, that knowledge was not being translated into practice. Logistic regression analysis showed that frequency of deworming, animal husbandry practice, contact with untreated animals, and treatment-seeking behaviors were significantly associated with parasitic infection. Conclusion: Several types of zoonotic parasites are widely prevalent in animals of Bangladesh and pose a potential risk to human health. This study highlights the need to diagnose animal parasitic infection and intensified case management to avoid spillovers to animals and humans.

Imported fascioliasis in Spain: Report of 12 cases from the +REDIVI collaborative network (2009-2019).

Torrús-Tendero, D., Ramos-Rincón, J., Salvador, F., Oliveira, I., Llenas-García, J., Arsuaga, M., Crespillo-Andújar, C., Pérez-Molina, J.
26-02-2022
Travel Med Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35227864

Background: There are few reports of imported fascioliasis in Spain. This study aimed to describe the characteristics of cases registered in +REDIVI network. Methods: Observational, retrospective, descriptive study of imported fascioliasis cases registered in the +REDIVI, a multicenter collaborative network collecting information on imported infectious diseases in Spain, from October 2009 to May 2019. Results: Of 25,203 cases of imported disease registered over the study period, 16 (0.063%) were fascioliasis, acquired mainly in Pakistan, Morocco, Bolivia, and Peru. Clinical, analytical, and therapeutic data were available for 12 cases (6 immigrants, 4 people visiting friends and relatives, 2 travelers). Eleven (91.6%) had eosinophilia. The most frequent symptoms were abdominal pain (n = 5) and cough (n = 5). Two cases (16.66%) were acute and 10 (83.33%) chronic. Two patients presented lung involvement, and four had other parasitic co-infections. Twelve cases (100%) were seropositive for Fasciola hepatica. Ten patients underwent a coproparasitological study, none of which detected Fasciola spp. eggs. The probable food origin (watercress) was confirmed in 3 cases (25%). Nine of the 10 patients treated with triclabendazole (90%) and one patient treated with praziquantel were considered to meet the criteria for cure. One patient was lost to follow-up. Conclusions: Fascioliasis is a rare imported parasitosis in Spain. Eosinophilia, along with geographical origin, is the main clue for diagnosis.

FILARIOSE LYMPHATIQUE

A call for loiasis to be added to the WHO list of neglected tropical diseases.

Revue de littérature

Jacobsen, K., Andress, B., Bhagwat, E., Bryant, C., Chandrapu, V., Desmonts, C., Matthews, T., Ogunkoya, A., Wheeler, T., Williams, A.
29-04-2022
Lancet Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35500592

Loiasis, also called African eye worm, is not currently on WHO's list of priority neglected tropical diseases, even though the risk that individuals with high Loa loa microfilarial densities will develop potentially fatal encephalopathy when they take ivermectin has complicated efforts to use mass drug administration for onchocerciasis (river blindness) and lymphatic filariasis control in co-endemic areas. At least 10 million residents of central and west Africa are thought to have loiasis, which causes painful and itchy subcutaneous oedema, arthralgia, and discomfort when adult helminths that are 3-7 cm in length are present under the conjunctiva of the eye. High levels of microfilaraemia are associated with renal, cardiac, neurological, and other sequelae, and an increased risk of death. The public health burden of loiasis could be greatly reduced with expanded use of diagnostic tests, anthelmintic treatment, and control of the Chrysops spp (tabanid flies) vectors that transmit the parasite. Loiasis should be added to the next revision of the WHO neglected tropical disease priority list, not merely because its inclusion will support the elimination of other skin and subcutaneous neglected tropical diseases, but also because of the complications caused by loiasis itself.

Bma-LAD-2, an Intestinal Cell Adhesion Protein, as a Potential Therapeutic Target for Lymphatic Filariasis.

Flynn, A., Taylor, R., Pazgier, M., Bennuru, S., Lindrose, A., Sterling, S., Morris, C., Gleeson, B., Maugel, T., Nutman, T., Mitre, E.
27-04-2022
mBio
https://doi.org/10.1128/mbio.03742-21

Lymphatic filariasis is a debilitating disease that afflicts over 70 million people worldwide. It is caused by the parasitic nematodes Wuchereria bancrofti, Brugia malayi, and Brugia timori. Despite substantial success, efforts to eliminate LF will likely require more time and resources than predicted. Identifying new drug and vaccine targets in adult filariae could help elimination efforts. This study's aim was to evaluate intestinal proteins in adult Brugia malayi worms as possible therapeutic targets. Using short interfering RNA (siRNA), we successfully targeted four candidate gene transcripts: Bma-Serpin, Bma-ShTK, Bma-Reprolysin, and Bma-LAD-2. Of those, Bma-LAD-2, an immunoglobulin superfamily cell adhesion molecule (IgSF CAM), was determined to be essential for adult worm survival. We observed a 70.42% knockdown in Bma-LAD-2 transcript levels 1 day post-siRNA incubation and an 87.02% reduction in protein expression 2 days post-siRNA incubation. This inhibition of Bma-LAD-2 expression resulted in an 80% decrease in worm motility over 6 days, a 93.43% reduction in microfilaria release (Mf) by day 6 post-siRNA incubation, and a dramatic decrease in (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction. Transmission electron microscopy revealed the loss of microvilli and unraveling of mitochondrial cristae in the intestinal epithelium of Bma-LAD-2 siRNA-treated worms. Strikingly, Bma-LAD-2 siRNA-treated worms exhibited an almost complete loss of pseudocoelomic fluid. A luciferase immunoprecipitation system assay did not detect anti-Bma-LAD-2 IgE in the serum of 30 LF patients, indicating that LF exposure does not result in IgE sensitization to this antigen. These results indicate that Bma-LAD-2 is an essential protein for adult Brugia malayi and may be an effective therapeutic target. IMPORTANCE Brugia malayi is a parasitic nematode that can cause lymphatic filariasis, a debilitating disease prevalent in tropical and subtropical countries. Significant progress has been made toward eliminating the disease. However, complete eradication may require new therapeutics such as drugs or a vaccine that kill adult filariae. In this study, we identified an immunoglobulin superfamily cell adhesion molecule (Bma-LAD-2) as a potential drug and vaccine candidate. When we knocked down Bma-LAD-2 expression, we observed a decrease in worm motility, fecundity, and metabolism. We also visualized the loss of microvilli, destruction of the mitochondria in the intestinal epithelium, and loss of pseudocoelomic fluid contents after Bma-LAD-2 siRNA treatment. Finally, we demonstrated that serum from filaria-infected patients does not contain preexisting IgE to Bma-LAD-2, which indicates that this antigen would be safe to administer as a vaccine in populations where the disease is endemic.

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

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

Host-parasite interaction has always been an area of interest to the parasite biologists. The complex immune interactions between the parasite and/or the parasite-derived products with the host immune cells determine the fate of the disease biology. Parasitic organisms are widely equipped with a vast array of protective machineries including antioxidant enzymes to withstand the hostile condition inside the host body. The reactive oxygen species (ROS) generated inside the host as a result of parasitic intervention can be endured by the parasite by their own tools to ensure their survival. One such antioxidant enzyme in the filarial parasite that plays a significant role in redox homeostasis, survivability and disease progression is the thioredoxin reductase (TrxR). Herein, we have projected a crude lysate of the bovine filarial parasite

Setaria cervi enriched with high TrxR enzyme activity has the capacity to downregulate lipopolysaccharide (LPS)-induced inflammatory macrophages. TrxR-mediated inhibition of the TLR4-NF-κB axis resulting into downregulation of the pro-inflammatory cytokines with concomitant upregulation of the anti-inflammatory cytokines supports the filarial parasite to produce an anti-inflammatory milieu which ultimately promotes worm survivability inside the host and pathogenesis.

Biochemical and structural characterizations of thioredoxin reductase selenoproteins of the parasitic filarial nematodes Brugia malayi and Onchocerca volvulus.

Fata, F., Gencheva, R., Cheng, Q., Lullo, R., Ardini, M., Silvestri, I., Gabriele, F., Ippoliti, R., Bulman, C., Sakanari, J., Williams, D., Arnér, E., Angelucci, F.
04-03-2022
Redox Biol
https://pubmed.ncbi.nlm.nih.gov/35276442

Enzymes in the thiol redox systems of microbial pathogens are promising targets for drug development. In this study we characterized the thioredoxin reductase (TrxR) selenoproteins from Brugia malayi and Onchocerca volvulus, filarial nematode parasites and causative agents of lymphatic filariasis and onchocerciasis, respectively. The two filarial enzymes showed similar turnover numbers and affinities for different thioredoxin (Trx) proteins, but with a clear preference for the autologous Trx. Human TrxR1 (hTrxR1) had a high and similar specific activity versus the human and filarial Trxs, suggesting that, in vivo, hTrxR1 could possibly be the reducing agent of parasite Trxs once they are released into the host. Both filarial TrxRs were efficiently inhibited by auranofin and by a recently described inhibitor of human TrxR1 (TRi-1), but not as efficiently by the alternative compound TRi-2. The enzyme from B. malayi was structurally characterized also in complex with NADPH and auranofin, producing the first crystallographic structure of a nematode TrxR. The protein represents an unusual fusion of a mammalian-type TrxR protein architecture with an N-terminal glutaredoxin-like (Grx) domain lacking typical Grx motifs. Unlike thioredoxin glutathione reductases (TGRs) found in platyhelminths and mammals, which are also Grx-TrxR domain fusion proteins, the TrxRs from the filarial nematodes lacked glutathione disulfide reductase and Grx activities. The structural determinations revealed that the Grx domain of TrxR from B. malayi contains a cysteine (C22), conserved in TrxRs from clade IIIc nematodes, that directly interacts with the C-terminal cysteine-selenocysteine motif of the homo-dimeric subunit. Interestingly, despite this finding we found that altering C22 by mutation to serine did not affect enzyme catalysis. Thus, although the function of the Grx domain in these filarial TrxRs remains to be determined, the results obtained provide insights on key properties of this important family of selenoprotein flavoenzymes that are potential drug targets for treatment of filariasis.

Potential inhibitors for peroxiredoxin 6 of W. bancrofti: A combined study of modelling, structure-based drug design and MD simulation.

Sureshan, M., Prabhu, D., Aruldoss, I., Saraboji, K.
30-12-2021
J Mol Graph Model
https://pubmed.ncbi.nlm.nih.gov/34990985

Lymphatic filariasis (LF), a mosquito-borne parasitic disease caused by nematode Wuchereria bancrofti in tropical and sub-tropical countries. These nematodes are transferred into the human host when the infected mosquito carrying L3 larvae is released into the bloodstream during the blood ingestion process. The host immune system produces ROS (Reactive Oxygen Species) as a primary defence mechanism to remove the invading filarial worms. However, well-defined antioxidant enzymes of the nematodes scavenge the host-produced ROS to escape from oxidative stress. The enzyme peroxiredoxin 6 (Prx6) belongs to the peroxiredoxin family, catalyses hydrogen peroxide (H_2O_2) into water (H_2O). In order to find the inhibitors that inhibit the activity of peroxiredoxin 6 of W. bancrofti. We performed the homology modelling to predict the WbPrx6 three-dimensional structure using the Schrödinger-Prime and the dynamic stability of the modelled WbPrx6 was analyzed by carrying out the molecular dynamic (MD) simulation for the time scale of 200ns. Further, the structure-based virtual screening shortlisted the hit molecules from the ChemBridge database based on the glide score. The potential lead molecules (ID: 10239274, 11112883, 79879205, 58160895, and 42133744) that have better binding and satisfied the ADMET properties were selected for further complex simulation and DFT calculations. The identified compounds interact with the N-terminal region of the thioredoxin domain, which plays a key role in reducing phospholipase A2 activity. Interestingly, upon binding the lead molecule, the fluctuation of the loop region that connects α-IV with the β-VI plays a vital role in affecting the geometry of the active site, which in turn affects the activity WbPrx6. The outcomes of the present computational studies could help in future drug development and designing of the effective candidate to control Lymphatic filariasis.

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.

ONCHOCERCOSE

Anti-Th17 and anti-Th2 responses effects of hydro-ethanolic extracts of Aframomum melegueta, Khaya senegalensis and Xylopia aethiopica in hyperreactive onchocerciasis individuals' peripheral blood mononuclear cells.

Katawa, G., Ataba, E., Ritter, M., Amessoudji, O., Awesso, E., Tchadié, P., Bara, F., Douti, F., Arndts, K., Tchacondo, T., Batawila, K., Ameyapoh, Y., Hoerauf, A., Karou, S., Layland, L.
25-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010341

Hyperreactive onchocerciasis (HO) is characterized by a severe skin inflammation with elevated Th17-Th2 combined responses. We previously demonstrated the anthelminthic activity of Aframomum melegueta (AM), Xylopia aethiopica (XA) and Khaya senegalensis (KS) used by traditional healers to treat helminthiasis in the endemic area of Togo. However, their effect on severe onchocerciasis is poorly investigated. The present study aimed to investigate the anti-Th17 and anti-Th2 effects of hydro-ethanolic extracts of AM, XA and KS during HO. Onchocerca volvulus-infected individuals were recruited in the Central region of Togo in 2018. Isolated peripheral blood mononuclear cells (PBMCs) from both generalized onchocerciasis (GEO) and HO forms were activated with anti-CD3 and anti-CD28 monoclonal antibodies in the presence or absence of the hydro-ethanolic extracts of AM, XA and KS as well as their delipidated, deproteinized and deglycosylated fractions. After 72 hours, cytokines were assayed from cell culture supernatants. Then, flow cytometry was used to investigate the effects of the extracts on cell activation, proliferation, intracellular cytokines and T cells transcription factors. The production of both Th17 and Th2 cytokines IL-17A and IL-5 were significantly inhibited upon T-cell receptor (TCR) activation in the presence of the hydro-ethanolic extracts of AM, XA and KS in HO individuals' PBMCs in vitro. AM and XA inhibited CD4+RORC2+IL-17A+ and CD4+GATA3+IL-4+ cell populations induction. This inhibition was not Th1 nor Treg-dependent since both IFN-γ and IL-10 were also inhibited by the extracts. AM and XA did not interfere with T cell activation and proliferation for their inhibitory pathways. Lipid and protein compounds from AM and XA were associated with the inhibition of IL-17A. This study showed that in addition to their anthelminthic effects, hydro-ethanolic extracts of Aframomum melegueta, Xylopia aethiopica and Khaya senegalensis could downregulate both Th17 and Th2 responses and prevent the severe skin disorder observed.

Biochemical and structural characterizations of thioredoxin reductase selenoproteins of the parasitic filarial nematodes Brugia malayi and Onchocerca volvulus.

Fata, F., Gencheva, R., Cheng, Q., Lullo, R., Ardini, M., Silvestri, I., Gabriele, F., Ippoliti, R., Bulman, C., Sakanari, J., Williams, D., Arnér, E., Angelucci, F.
04-03-2022
Redox Biol
https://pubmed.ncbi.nlm.nih.gov/35276442

Enzymes in the thiol redox systems of microbial pathogens are promising targets for drug development. In this study we characterized the thioredoxin reductase (TrxR) selenoproteins from Brugia malayi and Onchocerca volvulus, filarial nematode parasites and causative agents of lymphatic filariasis and onchocerciasis, respectively. The two filarial enzymes showed similar turnover numbers and affinities for different thioredoxin (Trx) proteins, but with a clear preference for the autologous Trx. Human TrxR1 (hTrxR1) had a high and similar specific activity versus the human and filarial Trxs, suggesting that, in vivo, hTrxR1 could possibly be the reducing agent of parasite Trxs once they are released into the host. Both filarial TrxRs were efficiently inhibited by auranofin and by a recently described inhibitor of human TrxR1 (TRi-1), but not as efficiently by the alternative compound TRi-2. The enzyme from B. malayi was structurally characterized also in complex with NADPH and auranofin, producing the first crystallographic structure of a nematode TrxR. The protein represents an unusual fusion of a mammalian-type TrxR protein architecture with an N-terminal glutaredoxin-like (Grx) domain lacking typical Grx motifs. Unlike thioredoxin glutathione reductases (TGRs) found in platyhelminths and mammals, which are also Grx-TrxR domain fusion proteins, the TrxRs from the filarial nematodes lacked glutathione disulfide reductase and Grx activities. The structural determinations revealed that the Grx domain of TrxR from B. malayi contains a cysteine (C22), conserved in TrxRs from clade IIIc nematodes, that directly interacts with the C-terminal cysteine-selenocysteine motif of the homo-dimeric subunit. Interestingly, despite this finding we found that altering C22 by mutation to serine did not affect enzyme catalysis. Thus, although the function of the Grx domain in these filarial TrxRs remains to be determined, the results obtained provide insights on key properties of this important family of selenoprotein flavoenzymes that are potential drug targets for

treatment of filariasis.

SCHISTOSOMIASE

A low dose adenovirus vectored vaccine expressing Schistosoma mansoni Cathepsin B protects from intestinal schistosomiasis in mice.

Perera, D., Hassan, A., Liu, S., Elahi, S., Gadoury, C., Weeratna, R., Gilbert, R., Ndao, M.
29-04-2022
EBioMedicine
https://pubmed.ncbi.nlm.nih.gov/35500538

Background: Schistosomiasis is an underestimated neglected tropical disease which affects over 236.6 million people worldwide. According to the CDC, the impact of this disease is second to only malaria as the most devastating parasitic infection. Affected individuals manifest chronic pathology due to egg granuloma formation, destroying the liver over time. The only FDA approved drug, praziquantel, does not protect individuals from reinfection, highlighting the need for a prophylactic vaccine. Schistosoma mansoni Cathepsin B (SmCB) is a parasitic gut peptidase necessary for helminth growth and maturation and confers protection as a vaccine target for intestinal schistosomiasis. Methods: An SmCB expressing human adenovirus serotype 5 (AdSmCB) was constructed and delivered intramuscularly to female C57BL/6 mice in a heterologous prime and boost vaccine with recombinant protein. Vaccine induced immunity was described and subsequent protection from parasite infection was assessed by analysing parasite burden and liver pathology. Findings: Substantially higher humoral and cell-mediated immune responses, consisting of IgG2c, Th1 effectors, and polyfunctional $CD4^+$ T cells, were induced by the heterologous administration of AdSmCB when compared to the other regimens. Though immune responses favoured Th1 immunity, Th2 responses provided by SmCB protein boosts were maintained. This mixed Th1/Th2 immune response resulted in significant protection from S. mansoni infection comparable to other vaccine formulations which are in clinical trials. Schistosomiasis associated liver pathology was also prevented in a murine model. Interpretation: Our study provides missing preclinical data supporting the use of adenoviral vectoring in vaccines for S. mansoni infection. Our vaccination method significantly reduces parasite burden and its associated liver pathology - both of which are critical considerations for this helminth vaccine. Funding: This work was supported by the Canadian Institutes of Health Research, R. Howard Webster Foundation, and the Foundation of the McGill University Health Centre.

Comparing the accuracy of two diagnostic methods for detection of light Schistosoma haematobium infection in an elimination setting in Wolaita Zone, South Western Ethiopia.

Mohammed, H., Landeryou, T., Chernet, M., Liyew, E., Wulataw, Y., Getachew, B., Difabachew, H., Phillips, A., Maddren, R., Ower, A., Mekete, K., Belay, H., Endrias, T., Anjulo, U., Tasew, G., Anderson, R., Tollera, G., Abate, E.
29-04-2022
PLoS One
https://doi.org/10.1371/journal.pone.0267378

Reagent urinalysis dipstick and filtration have been recommended diagnostic methods for the detection of urogenital schistosomiasis. However, the accurate diagnosis of light infections using these methods presents a major challenge. This study evaluates the diagnosis accuracy of light infection with Schistosoma haematobium in study participants living in Wolaita Zone, an area targeted for sustainable control of Schistosomiasis, and ultimately interrupt transmission. Urine samples were collected from children and adults in surveys carried out during baseline and longitudinal sentinel site surveys conducted from 2018 to 2020. All urine samples were tested using a reagent urinalysis dipstick test (Haemastix) to detect microhaematuria with reference urine filtration technique as a proxy for S. haematobium infection. Sensitivity and specificity were determined in diagnosing urogenital schistosomiasis. Cohen's Kappa statistics was done for the agreement of these diagnostic methods. A total of 12,102 participants were enrolled in the current baseline study. Among them, 285 (2.35%) samples tested positive for microhaematuria and 21 (0.20%) positive for S. haematobium eggs. A total of 4,357 samples were examined in year 1 and year 2 using urine dipsticks, and urine filtration 172 (3.95%) and 2 (0.05%) were positive for microhaematuria and S. haematobium eggs. The reagent urinalysis dipsticks showed the highest sensitivity and specificity for diagnosing light intensity of infection,100% (95% CI:85.18-100.00) and 97.4% (95% CI: 97.10-97.60), respectively. There is a slight agreement between the two methods (Kappa = 0.09, 95% CI: 0.01-0.18). The present study revealed very low prevalence and light intensity of S. haematobium infections. The study also highlights that the dipstick test is considered a useful adjunct diagnostic tool for population-based control of urogenital schistosomiasis.

The observed relationship between the degree of parasite aggregation and the prevalence of infection within human host populations for soil-transmitted helminth and schistosome infections.

Kura, K., Truscott, J., Collyer, B., Phillips, A., Garba, A., Anderson, R.
26-04-2022
Trans R Soc Trop Med Hyg
https://pubmed.ncbi.nlm.nih.gov/35474017

Background: Soil-transmitted helminths (STH) and schistosome parasites are highly aggregated within the human population. The probability distribution of worms per person is described

well by the negative binomial probability distribution with aggregation parameter, k, which varies inversely with parasite clustering. The relationship between k and prevalence in defined populations subject to mass drug administration is not well understood. **Methods and results:** We use statistical methods to estimate k using two large independent datasets for STH and schistosome infections from India and Niger, respectively, both of which demonstrate increased aggregation of parasites in a few hosts, as the prevalence of infections declines across the dataset. **Conclusions:** A greater attention needs to be given in monitoring and evaluation programmes to find and treat the remaining aggregates of parasites.

Infection intensity-dependent accuracy of reagent strip for the diagnosis of Schistosoma haematobium and estimation of treatment prevalence thresholds.

Grolimund, C., Bärenbold, O., Hatz, C., Vennervald, B., Mayombana, C., Mshinda, H., Utzinger, J., Vounatsou, P.
25-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010332

Background: Reagent strip to detect microhematuria as a proxy for Schistosoma haematobium infections has been considered an alternative to urine filtration for individual diagnosis and community-based estimates of treatment needs for preventive chemotherapy. However, the diagnostic accuracy of reagent strip needs further investigation, particularly at low infection intensity levels. **Methods:** We used existing data from a study conducted in Tanzania that employed urine filtration and reagent strip testing for S. haematobium in two villages, including a baseline and six follow-up surveys after praziquantel treatment representing a wide range of infection prevalence. We developed a Bayesian model linking individual S. haematobium egg count data based on urine filtration to reagent strip binary test results available on multiple days and estimated the relation between infection intensity and sensitivity of reagent strip. Furthermore, we simulated data from 3,000 hypothetical populations with varying mean infection intensity to infer on the relation between prevalence observed by urine filtration and the interpretation of reagent strip readings. **Principal findings:** Reagent strip showed excellent sensitivity even for single measurement reaching 100% at around 15 eggs of S. haematobium per 10 ml of urine when traces on reagent strip were considered positive. The corresponding specificity was 97%. When traces were considered negative, the diagnostic accuracy of the reagent strip was equivalent to urine filtration data obtained on a single day. A 10% and 50% urine filtration prevalence based on a single day sampling corresponds to 11.2% and 48.6% prevalence by reagent strip, respectively, when traces were considered negative, and 17.6% and 57.7%, respectively, when traces were considered positive. **Conclusions/Significance:** Trace results should be included in reagent strip readings when high sensitivity is required, but excluded when high specificity is needed. The observed prevalence of reagent strip results, when traces are considered negative, is a good proxy for prevalence estimates of S. haematobium infection by urine filtration on a single day.

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

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

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

Recombinant P40 protein of Schistosoma japonicum inhibits TREM-1 expression in RAW264.7 cells via FOXO3a.

Shen, P., Zhang, T., Chen, G., Zhang, B., Huang, A., Duan, L., Zhu, D., Chen, J., Wang, J., Duan, Y.
17-03-2022
Biomed Pharmacother
https://pubmed.ncbi.nlm.nih.gov/35306429

Triggering receptor expressed on myeloid cells 1 (TREM-1) is a transmembrane glycoprotein receptor and TREM-1 expression reached the peak at 6 weeks after infection with Schistosoma japonicum and inhibited subsequently. Since TREM-1 may be involved in the macrophage polarization process, the reason for the inhibition of TREM-1 expression in chronic schistosomiasis engaged us in them. In this study, flow cytometry was used to observe TREM-1 expression in peritoneal macrophages from mice infected with Schistosoma japonicum. Since P40 is one of the main components from schistosoma eggs, western blot and dual-luciferase reporter assays were performed to observe the effect of recombinant Schistosoma japonicum P40 protein (rSjP40) on TREM-1 expression in the mouse leukemic monocyte/macrophage cell line RAW264.7. These methods were also conducted to observe the effect of FOXO3a on the expression of TREM-1 in

RAW264.7 cells, and a ChIP assay was performed to confirm the binding site of FOXO3a to the TREM-1 promoter. Our results showed that TREM-1 expression reached the peak in peritoneal macrophages from mice at 6 weeks after infection with Schistosoma japonicum. rSjP40 inhibited TREM-1 promoter activity at the position of - 1924 ~ - 1531 bp. rSjP40 down-regulated TREM-1 and FOXO3a protein expression in RAW264.7 cells. TREM-1 protein expression may be regulated by binding of FOXO3a to the promoter of TREM-1 in RAW264.7 cells. In conclusion, we found that rSjP40 inhibited TREM-1 expression in macrophages by inhibiting FOXO3a expression. This study will provide the basis for the study to explore the role of TREM-1 in Schistosoma japonicum infection.

Screening for parasites in migrant children.

Bustamante, J., Sainz, T., Ara-Montojo, M., Almirón, M., Subirats, M., Vega, D., Mellado, M., López-Hortelano, M.
15-03-2022
Travel Med Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35304329

Background: Globalization has pushed population movements in the last decades, turning imported diseases into the focus. Due to behavioral habits, children are at higher risk of acquiring parasitosis. This study aims to investigate the prevalence of parasites in migrant children and factors associated with parasitic diseases. Method: Retrospective cross-sectional study (2014-2018) including children diagnosed with parasitosis. The diagnosis was based on serology and/or microscopic stool-sample evaluation. Epidemiological and clinical data were recorded. Results: Out of 813 migrant children screened, 241 (29.6%) presented at least one parasite, and 89 (10.9%) more than one. The median age was 6.6 years (IQR: 3.1-11.9) and 58.9% were males. Most cases were referred for a health exam; only 52.3% of children were symptomatic, but 43.6% had eosinophilia. The most common diagnosis were giardiasis (35.3%), schistosomiasis (19.1%), toxocariasis (15.4%), and strongyloidiasis (9.1%). After the multivariate analysis, African origin and presenting with eosinophilia were the main risk factors for parasitism. Conclusions: parasitosis are frequent among migrant children. Children are often asymptomatic, and thus active screening for parasitosis should be considered among high-risk populations. Eosinophilia can be useful to guide complimentary tests, as well as geographical origin, but normal eosinophil count does not exclude parasitosis.

Insights on the Gut-Mesentery-Lung Axis in Pulmonary Arterial Hypertension: A Poorly Investigated Crossroad.

Revue de littérature

Oliveira, S.
17-03-2022
Arterioscler Thromb Vasc Biol
https://doi.org/10.1161/ATVBAHA.121.316236

Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by the hyperproliferation of vascular cells, including smooth muscle and endothelial cells. Hyperproliferative cells eventually obstruct the lung vasculature, leading to irreversible lesions that collectively drive pulmonary pressure to life-threatening levels. Although the primary cause of PAH is not fully understood, several studies have indicated it results from chronic pulmonary inflammation, such as observed in response to pathogens' infection. Curiously, infection by the intravascular parasite Schistosoma mansoni recapitulates several aspects of the widespread pulmonary inflammation that leads to development of chronic PAH. Globally, >200 million people are currently infected by *Schistosoma spp.*, with about 5% developing PAH (Sch-PAH) in response to the parasite egg-induced obliteration and remodeling of the lung vasculature. Before their settling into the lungs, Schistosoma eggs are released inside the mesenteric veins, where they either cross the intestinal wall and disturb the gut microbiome or migrate to other organs, including the lungs and liver, increasing pressure. Spontaneous or surgical liver bypass via collateral circulation alleviates the pressure in the portal system; however, it also allows the translocation of pathogens, toxins, and antigens into the lungs, ultimately causing PAH. This brief review provides an overview of the gut-mesentery-lung axis during PAH, with a particular focus on Sch-PAH, and attempts to delineate the mechanism by which pathogen translocation might contribute to the onset of chronic pulmonary vascular diseases.

Metagenome-Assembled Genomes Reveal Mechanisms of Carbohydrate and Nitrogen Metabolism of Schistosomiasis-Transmitting Vector *Biomphalaria Glabrata*.

Du, S., Sun, X., Zhang, J., Lin, D., Chen, R., Cui, Y., Xiang, S., Wu, Z., Ding, T.
07-03-2022
Microbiol Spectr
https://doi.org/10.1128/spectrum.01843-21

Biomphalaria glabrata transmits schistosomiasis mansoni which poses considerable risks to hundreds of thousands of people worldwide, and is widely used as a model organism for studies on the snail-schistosome relationship. Gut microbiota plays important roles in multiple aspects of host including development, metabolism, immunity, and even behavior; however, detailed information on the complete diversity and functional profiles of *B. glabrata* gut microbiota is still limited. This study is the first to reveal the gut microbiome of *B. glabrata* based on metagenome-assembled genome (MAG). A total of 28 gut samples spanning diet and age were sequenced and 84 individual microbial genomes with≥70% completeness and≤5% contamination were constructed. *Bacteroidota* and *Proteobacteria* were the dominant bacteria in the freshwater snail, unlike terrestrial organisms harboring many species of *Firmicutes* and *Bacteroidota*. The microbial consortia in *B. glabrata* helped in the digestion of complex polysaccharide

such as starch, hemicellulose, and chitin for energy supply, and protected the snail from food poisoning and nitrate toxicity. Both microbial community and metabolism of *B. glabrata* were significantly altered by diet. The polysaccharide-degrading bacterium *Chryseobacterium* was enriched in the gut of snails fed with high-digestibility protein and high polysaccharide diet (HPHP). Notably, *B. glabrata* as a mobile repository can escalate biosafety issues regarding transmission of various pathogens such as Acinetobacter nosocomialis and Vibrio parahaemolyticus as well as multiple antibiotic resistance genes in the environment and to other organisms. IMPORTANCE The spread of aquatic gastropod *Biomphalaria glabrata*, an intermediate host of Schistosoma mansoni, exacerbates the burden of schistosomiasis disease worldwide. This study provides insights into the importance of microbiome for basic biological activities of freshwater snails, and offers a valuable microbial genome resource to fill the gap in the analysis of the snail-microbiota-parasite relationship. The results of this study clarified the reasons for the high adaptability of *B. glabrata* to diverse environments, and further illustrated the role of *B. glabrat*a in accumulation of antibiotic resistance in the environment and spread of various pathogens. These findings have important implications for further exploration of the control of snail dissemination and schistosomiasis from a microbial perspective.

A genetic TRP down the channel to praziquantel resistance.

Cotton, J., Doyle, S.
01-03-2022
Trends Parasitol
https://pubmed.ncbi.nlm.nih.gov/35246385

The anthelmintic praziquantel (PZQ) is an essential tool in controlling schistosomiasis, so reports of reduced PZQ efficacy are of great public health concern. Le Clec'h et al. recently identified a gene responsible for PZQ resistance in experimentally selected resistant Schistosoma mansoni. The importance of this locus in natural infections remains to be established.

Differential proteomic analysis of laser-microdissected penetration glands of avian schistosome cercariae with a focus on proteins involved in host invasion.

Vondráček, O., Mikeš, L., Talacko, P., Leontovyč, R., Bulantová, J., Horák, P.
23-02-2022
Int J Parasitol
https://pubmed.ncbi.nlm.nih.gov/35218763

Schistosome invasive stages, cercariae, leave intermediate snail hosts, penetrate the skin of definitive hosts, and transform to schistosomula which migrate to the final location. During invasion, cercariae employ histolytic and other bioactive products of specialized holocrine secretory cells - postacetabular (PA) and circumacetabular (CA) penetration glands. Although several studies attempted to characterize protein composition of the in vitro-induced gland secretions in Schistosoma mansoni and Schistosoma japonicum, the results were somewhat inconsistent and dependent on the method of sample collection and processing. Products of both gland types mixed during their secretion did not allow localization of identified proteins to a particular gland. Here we compared proteomes of separately isolated cercarial gland cells of the avian schistosome Trichobilharzia szidati, employing laser-assisted microdissection and shotgun LC-MS/MS, thus obtaining the largest dataset so far of the representation and localization of cercarial penetration gland proteins. We optimized the methods of sample processing with cercarial bodies (heads) first. Alizarin-pre-stained, chemically non-fixed samples provided optimal results of MS analyses, and enabled us to distinguish PA and CA glands for microdissection. Using 7.5×10^6 µm^3 sample volume per gland replicate, we identified 3347 peptides assigned to 792 proteins, from which 461 occurred in at least two of three replicates in either gland type (PA = 455, 40 exclusive; CA = 421, six exclusive; 60 proteins differed significantly in their abundance between the glands). Peptidases of five catalytic types accounted for ca. 8% and 6% of reliably identified proteins in PA and CA glands, respectively. Invadolysin, nardilysin, cathepsins B2 and L3, and elastase 2b orthologs were the major gland endopeptidases. Two cystatins and a serpin were highly abundant peptidase inhibitors in the glands. While PA glands generally had rich enzymatic equipment, CA glands were conspicuously abundant in venom allergen-like proteins.

Snails, microbiomes, and schistosomes: a three-way interaction?

Le Clec'h, W., Nordmeyer, S., Anderson, T., Chevalier, F.
18-02-2022
Trends Parasitol
https://pubmed.ncbi.nlm.nih.gov/35190282

Aquatic snails, the intermediate hosts of schistosomes, harbor a diverse unexplored microbiome. We speculate that this may play a critical role in host-parasite interactions. We summarize our current knowledge of snail microbiomes and highlight future research priorities.

A single oral dose of celecoxib-loaded solid lipid nanoparticles for treatment of different developmental stages of experimental schistosomiasis mansoni.

Ibrahim, E., Abou-El-Naga, I., El-Temsahy, M., Elsawy, E., Makled, S., Mogahed, N.
12-02-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35157841

Schistosomiasis, a neglected tropical parasitic disease, is associated with severe pathology, mortality and economic loss. The treatment and control of schistosomiasis depends

mainly on a single dose of praziquantel (PZQ). Drug repurposing and nanomedicine attract great attention to improve anti-schistosomal therapy. Previously, we reported that celecoxib (CELE), the non-steroidal anti-inflammatory drug, showed potent anti-schistosomal efficacy in an oral dose of 20 mg/kg/day for five days against different developmental stages of Schistosoma mansoni (S. mansoni) infection in mice. The aim of the current study was to shorten the duration of CELE treatment to reach an effective single oral dose against different developmental stages of S. mansoni infection using solid lipid nanoparticles (SLNs) as nano-carriers. The latter enhance the solubility, bioavailability and drug delivery and hence can decrease the frequency of administration which is of great clinical value. CELE-loaded SLNs showed good colloidal properties, high entrapment efficiency and drug loading, sustained biphasic release pattern with excellent storage stability. The used regimen was efficient against different developmental stages of S. mansoni infection with the most pronounced effect against the juvenile stage where the worm load, the hepatic egg count and the intestinal egg count were reduced by 86.39%, 91.45% and 90.11%, respectively. Meanwhile, when targeting the invasive and the adult stages, it induced reduction in the worm load by 73.55% and 78.22%, the hepatic egg count by 69.99% and 75.39% and the intestinal egg count by 77.57% and 79.89%, respectively. Additionally, CELE-loaded SLNs caused extensive tegumental damage of adult worms and marked improvement in the liver pathology.

Description and evaluation of a pathway for unaccompanied asylum-seeking children.

Armitage, A., Cohen, J., Heys, M., Hardelid, P., Ward, A., Eisen, S.
16-10-2021
Arch Dis Child
https://doi.org/10.1136/archdischild-2021-322319

Objective: (1) To describe a novel integrated pathway for unaccompanied asylum-seeking children (UASC). (2) To evaluate a population engaged with this service. **Design:** Description of the integrated pathway (objective 1) and retrospective evaluation, using data from community paediatrics, infectious diseases (IDs) screening and a sexual health (SH) service (objective 2). **Setting:** Unlinked data were collected from three services across three National Health Service (NHS) trusts in London. **Patients:** All Camden UASC engaged with the service from 01 January 2016 to 30 March 2019. **Interventions:** A multidisciplinary approach prioritising the health needs of UASC including a childre and adolescent mental health service (CAMHS) clinican and a health improvement practitioner. There are low thresholds for onward referral and universal asymptomatic screening of UASC for ID. **Main outcome measures:** Data on demographics, unmet health needs and known outcomes. **Results:** Data were available for 101 UASC, 16% female, median age 16 years (range 14-17). Physical assault/abuse was reported in 67% and 13% disclosed sexual assault/abuse, including 38% of female UASC. Mental health symptoms were documented in 77%. IDs warranting treatment were identified in 41% including latent tuberculosis (25%) and schistosomiasis (13%). Interpreters were required for 97% and initial non-attendance rates at follow-up were 40% (ID) and 49% (SH). **Conclusions:** These data demonstrate high rates of historical physical and sexual assault/abuse, unmet physical, mental and emotional health needs among UASC and significant barriers to engaging with services. An integrated pathway has been successfully implemented and shown to deliver appropriate, joined-up care for UASC, consistent with current recommendations, with the potential to improve outcomes.

In silico inhibition of SGTP4 as a therapeutic target for the treatment of schistosomiasis.

Adekiya, T., Aruleba, R., Klein, A., Fadaka, A.
23-11-2020
J Biomol Struct Dyn
https://doi.org/10.1080/07391102.2020.1850363

Schistosomiasis is an infectious tropical disease caused by parasitic flatworm of the genus Schistosoma. This debilitating disease chronically infects about 200 million people globally and management relies on chemotherapy. Unfortunately, the solely available schistosomicide (praziquantel) against all forms of adult schistosmes has been faced with numerous drawbacks. Thus, there is an urgent need to design and develop a new regimen for schistosomiasis. In light of this, the current study focuses on inhibiting the schistosome glucose transporter 4 (SGTP4) as a therapeutic candidate for schistosomiasis. Several studies have revealed that Schistosoma parasites require an adequate amount of energy/glucose to survive. We modelled the 3D structure and subsequently used the homology model for docking with praziquantel (PZQ), Licochalcone A, Licarin and Harmonine. The docked complexes were subjected to molecular dynamics using Desmond system of Schrodinger software. Furthermore, the pharmacokinetic parameters of the ligands were investigated using the QikProp tool in the Schrodinger-2019-4 software suite. After performing all the computational analysis, our findings reveal that all four ligands were able to inhibit SGTP4 effectively through the higher glide G score (dock score) of -5.8 (-5.8), -6.5 (-6.4), -7.3 (-7.3) and -4.9 (-4.9) in kcal/mol for praziquantel, licochalcone A, licarin and harmonine respectively against the protein. The molecular simulation further confirmed that the stability of the complexes formed between the ligands and protein is excellent. More so, all the ligands fulfilled oral drugability of both the Lipinski's rule of five and Veber's rules.The findings in this present study provide new useful insights for the design of drugs which can serve as an alternative to praziquantel in the treatment of schistosomiasis through the inhibition of SGTP4.Communicated by Freddie R. Salsbury.

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

High infection rates for onchocerciasis and soil-transmitted helminthiasis in children under five not receiving preventive chemotherapy: a bottleneck to elimination.

Nana-Djeunga, H., Djune-Yemeli, L., Domche, A., Donfo-Azafack, C., Efon-Ekangouo, A., Lenou-Nanga, C., Nzune-Toche, N., Balog, Y., Bopda, J., Mbickmen-Tchana, S., Thirumalaisamy, V., Penlap-Beng, V., Ntoumi, F., Kamgno, J.
28-04-2022
Infect Dis Poverty
https://doi.org/10.1186/s40249-022-00973-1

Background: The current mainstay for control/elimination of onchocerciasis and soil-transmitted helminthiasis (STH) relies on ivermectin- and mebendazole/albendazole-based preventive chemotherapies. However, children under five years of age have been excluded in both research activities and control programs, because they were believed to have insignificant infection rates. There is therefore a need for up-to-date knowledge on the prevalence and intensity of STH and onchocerciasis infections in this age group. This study aimed at assessing the rates and intensities of onchocerciasis and STH infections in children under five years of age who are excluded from ivermectin- or mebendazole/albendazole-based preventive chemotherapies. Methods: A series of cross-sectional surveys was conducted in four Health Districts in the Centre and Littoral Regions of Cameroon between 2018 and 2019. All subjects aged 2 to 4 years, were screened for prevalence (or infection rate) and intensity [number of eggs per gram of stool (epg) or number of microfilariae per skin snip (mf/ss)] of STH and onchocerciasis infections respectively using the Kato-Katz and skin snip methodologies. Chi-square and the non-parametric tests (Mann Whitney and Kruskal Wallis) were used to compare infection rates and intensities of infections between Health Districts and genders, respectively. Results: A total of 421 children were enrolled in this study. The overall prevalence of onchocerciasis was 6.6% [95% confidence interval (CI): 4.3–9.9], ranging from 3.6% (in the Ntui Health District) to 12.2% (in the Bafia Health District). The intensity of infection ranged from 0.5 to 46 microfilariae per skin snip [median: 5; interquartile range (IQR): 2.25–8.5]. The overall prevalence of STH was 9.6% (95% CI: 6.5–13.9), with a high infection rate (29.6%) in the Akonolinga Health District. Two STH species (Ascaris lumbricoides and Trichuris trichiura) were found among infected individuals. The median intensities of STH infections were 1,992 epg (IQR: 210–28,704) and 96 epg (IQR: 48–168) for A. lumbricoides and T. trichiura, respectively. Conclusions: This study reveals that children<5 years of age are highly infected with STH and onchocerciasis, and could contribute to the spread of these diseases, perpetuating a vicious circle of transmission and hampering elimination efforts. These findings reveal the urgent need to provide (or scale) treatments (likely pediatric formulations) to these preschool-aged children, especially in areas of high transmission, to accelerate efforts to reach WHO 2030 target.

Prevalence of hookworm infections among stray dogs and molecular identification of hookworm species for the first time in Bangladesh.

Singh, R., Roy, B., Begum, N., Talukder, M.
13-03-2022
Vet Parasitol Reg Stud Reports
https://pubmed.ncbi.nlm.nih.gov/35431075

Hookworms are the most common and voracious blood-sucking parasites of the small intestines of mammalian hosts such as dogs, cats, ruminants and humans. Canine hookworms are endemic in the Southeast Asian countries including Bangladesh. There is scarcity of information on the prevalence of hookworms of stray dogs in Bangladesh. The present study determined the prevalence of canine hookworms using fecal examination followed by morphometric and molecular identification. Fecal samples were collected from 320 stray dogs living in rural areas of Mymensingh district (Gauripur upazila, Mymensingh sadar upazila and Tarakanda upazila) and hookworm eggs were identified using the flotation techniques. The overall prevalence of hookworm was 79.1% through microscopic examination. Estimated fecal prevalence was higher in Gauripur upazila (89.7%) followed by Mymensingh sadar upazila (84.8%) and Tarakanda upazila (53.2%). Five hookworm species were identified based on the morphometric examination, namely, Ancylostoma caninum, Ancylostoma ceylanicum, Ancylostoma tubaeforme, Ancylostoma braziliense and Ancylostoma duodenale, respectively. Polymerase Chain Reaction (PCR) was performed with the genomic DNA by targeting the 5.8S rRNA (~ 404 bp) and Cytochrome oxidase-1 (Cox 1, ~ 450 bp) and confirmed the identification for the first time in Bangladesh. This study reveals that stray dogs may act as reservoir hosts of human hookworm infection. Further detail molecular study is warranted to explore the genetic diversity of hookworms that infect both dogs and human in Bangladesh.

Association between allergic sensitization and intestinal parasite infection in schoolchildren in Gqeberha, South Africa.

Brandt, O., Wegenstein, B., Müller, I., Smith, D., Nqweniso, S., Adams, L., Müller, S., du Randt, R., Pühse, U., Gerber, M., Navarini, A., Utzinger, J., Labhardt, N., Schindler, C., Walter, C.
02-03-2022
Clin Exp Allergy
https://doi.org/10.1111/cea.14100

Background: Inconsistent data exist regarding the influence of parasitic infection on the prevalence of allergic sensitization and disorders. Objective: To investigate the impact of geohelminth and protozoan infections on sensitization patterns and allergic symptoms of children living in low-income communities in Gqeberha, South Africa. Methods: In a

cross-sectional study, 587 schoolchildren aged 8-12 years were recruited in June 2016 and screened for reactivity to common allergens by skin prick tests (SPTs) and for parasitic infections by stool examination. Additionally, questionnaires were completed to record allergic symptoms the children may have experienced. **Results:** Positive SPTs were found in 237/587 children (40.4%), and about one-third of whom were polysensitized. Sensitizations were most frequently detected against the house dust mites (HDM) Dermatophagoides spp. (31.9%) and Blomia tropicalis (21.0%). Infections with geohelminths (Ascaris lumbricoides, Trichuris trichiura) were found in 26.8% and protozoan infections (Giardia intestinalis, Cryptosporidia spp.) in 13.9% of study participants. Mixed logistic regression analyses revealed negative associations between parasite infection and sensitization to Blomia tropicalis (OR: 0.54, 95% CI 0.33-0.89) and to Dermatophagoides spp. (OR 0.65, 95% CI 0.43-0.96), and between protozoan infection and allergic sensitization to any aeroallergen, although these associations were not significant when adjusted for false discovery. Geohelminth infection and intensity of geohelminth infection were both associated with reduced risk of polysensitization (OR 0.41, 95% CI 0.21-0.86), and this association remained significant with adjustment for false discovery. Reported respiratory symptoms were associated with HDM sensitization (ORs from 1.54 to 2.48), but not with parasite infection. **Conclusions and clinical relevance:** Our data suggest that geohelminth infection and high geohelminth infection intensity are associated with a reduced risk of polysensitization.

GALE

Autosomal dominant epidermolysis bullosa simplex exacerbated by hyperkeratotic scabies.

Lin, Y., Tu, W., Hou, P., Huang, H., Chen, P., Chang, C., Lee, J., McGrath, J., Hsu, C.
02-05-2022
J Dermatol
https://doi.org/10.1111/1346-8138.16406

European scabies challenge: What about permethrin-resistant mites?

Mayer, K., Biedermann, T., Posch, C.
26-04-2022
J Eur Acad Dermatol Venereol
https://doi.org/10.1111/jdv.18181

Can ivermectin mass drug administrations to control scabies also reduce skin and soft tissue infections? Hospitalizations and primary care presentations lower after a large-scale trial in Fiji.

Middleton, J.
11-04-2022
Lancet Reg Health West Pac
https://doi.org/10.1016/j.lanwpc.2022.100454

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

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

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

Effects of the COVID-19 pandemic on head lice and scabies infestation dynamics: a population-based study in France.

Launay, T., Bardoulat, I., Lemaitre, M., Blanchon, T., Fardet, L.
05-01-2022
Clin Exp Dermatol

https://doi.org/10.1111/ced.15054

Background: Lockdowns and physical distancing have dramatically limited the circulation of SARS-CoV-2 and other common communicable infections. However, little is known about their impact on head lice and scabies. **Aim:** To assess the impact of the 2020 French National lockdowns (17 March-11 May 2020, and 30 October-15 December 2020) and physical distancing recommendations (from February 2020) on the dynamics of head lice and scabies infestations. **Methods:** The weekly sales of topical head lice treatments, topical scabies treatments and oral ivermectin were extracted from the database of the healthcare science company IQVIA (60% of all French retail pharmacies) and analysed over a 5-year period (March 2016-December 2020). A periodic regression model was fitted to drug sales before the COVID-19 period (2016-2019) and extrapolated to compare the observed sales in 2020 to the expected sales. **Results:** A decrease of the sales of tracer topical treatments for head lice and scabies was observed from March 2020, synchronously with the first French national lockdown. For the period March-December 2020, the mean reduction in observed vs. expected sales for head lice and scabies topical treatments was 44% and 14%, respectively. By contrast, although there was an observed decrease in oral ivermectin sales after March 2020, it was much lower (4%), probably because of studies reporting the potential positive effects of this drug on COVID-19 infection. **Conclusion:** COVID-19 lockdown and physical distancing reduce circulation of head lice and scabies in France. Further studies are needed to assess the long-term impact of these social behaviour changes.

MORSURES DE SERPENT

Snakebite victim profiles and treatment-seeking behaviors in two regions of Kenya: results from a health demographic surveillance system.

Larson, P., Ndemwa, M., Thomas, A., Tamari, N., Diela, P., Changoma, M., Mohamed, A., Larson, M., Ketenci, K., Goto, K., Kaneko, S.

29-04-2022
Trop Med Health
https://doi.org/10.1186/s41182-022-00421-8

Introduction: Snakebites are a major cause of permanent injury and death among poor, rural populations in developing countries, including those in East Africa. This research characterizes snakebite incidence, risk factors, and subsequent health-seeking behaviors in two regions of Kenya using a mixed methods approach. **Methods:** As a part of regular activities of a health demographic surveillance system, household-level survey on snakebite incidence was conducted in two areas of Kenya: Kwale along the Kenyan Coast and Mbita on Lake Victoria. If someone in the home was reported to have been bitten in the 5 years previous to the visit, a survey instrument was administered. The survey gathered contextual information on the bite, treatment-seeking behavior and clinical manifestations. To obtain deeper, contextual information, respondents were also asked to narrate the bite incident, subsequent behavior and outcomes. **Results:** 8775 and 9206 households were surveyed in Kwale and Mbita, respectively. Out of these, 453 (5.17%) and 92 (1.00%) households reported that at least one person had been bitten by a snake in the past 5 years. Deaths from snakebites were rare (4.04%), but patterns of treatment seeking varied. Treatment at formal care facilities were sought for 50.8% and at traditional healers for 53.3%. 18.4% sought treatment from both sources. Victims who delayed receiving treatment from a formal facility were more likely to have consulted a traditional healer (OR 8.8995% CI [3.83, 20.64]). Delays in treatment seeking were associated with significantly increased odds of having a severe outcome, including death, paralysis or loss of consciousness (OR 3.47 95% CI [1.56; 7.70]). **Conclusion:** Snakebite incidence and outcomes vary by region in Kenya, and treatment-seeking behaviors are complex. Work needs to be done to better characterize the spatial distribution of snakebite incidence in Kenya and efforts need to be made to ensure that victims have sufficient access to effective treatments to prevent death and serious injury.

Snakebite envenomation in children: An ongoing burden in Morocco.

Essafti, M., Fajri, M., Rahmani, C., Abdelaziz, S., Mouaffak, Y., Younous, S.

02-04-2022
Ann Med Surg (Lond)
https://doi.org/10.1016/j.amsu.2022.103574

Introduction: Snakebites are a leading cause of mortality and permanent disabilities especially among children in tropical countries and rural areas such as Morocco. Thus, a nationwide management protocol including specific antivenom therapy along with prevention strategies was implemented to reduce the overall snakebites morbimortality. **Patients and methods:** Our retrospective study aimed to describe the clinical aspects of snakebite envenomation before and after the implementation of this protocol in children admitted to the pediatric intensive care unit (PICU) in Marrakesh-Morocco for a period of 11 years. **Results:** A total of 75 cases were included and were mostly male (70%) with a mean age of 10 years old. Most envenomations were mild or severe (75%) and often occurred during outdoor activities in limb extremities. Altered hemostasis frequently occurred in 67% of cases but was rarely associated with severe exteriorized hemorrhage. Moderate anemia and PNN- predominant leukocytosis were often observed at admission (52.2% and 58%) but quickly tended to normalize before 48 h. Local symptoms were the main dread as they quickly evolve to a compartment syndrome and necrosis in the absence of antivenom therapy. Fasciotomy was performed in 33% of cases while 5 children required limb amputation. Antivenom administration (n = 39) was statistically significant for rapid improvement in hemostasis disorders, reduced blood transfusions and fasciotomy for

compartment syndrome as well as a shortened length of stay in PICU. The onset of acute kidney injury was observed in 18 cases but restored in most patients within 48 h (77%). Five children died of which only two had received delayed antivenom immunotherapy due to its unavailability and deferred hospital admission. **Conclusion:** The advent of specific serotherapy has made it possible to optimize the management of patients and to prevent and treat local and systemic complications thus improving the overall prognosis; nevertheless, primary prevention remains the key to reducing snakebites morbimortality.

Predictors of FabAV use in copperhead envenomation.

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06-01-2022

Clin Toxicol (Phila)

https://doi.org/10.1080/15563650.2021.2018454

Context: Crotaline snake envenomation is a serious medical condition affecting thousands of Americans each year. Variation in the treatment of Crotaline snakebites exists among physicians in the United States. Management of copperhead snakebites is controversial with some experts advocating minimal intervention, rarely necessitating antivenom use and, even more rarely, surgical intervention. This study assessed the use of Crotaline Polyvalent Immune Fab antivenom (Ovine) (FabAV) and explored factors influencing the decision to prescribe antivenom for copperhead envenomation in patients in Northeastern Oklahoma. **Methods:** A retrospective cohort study examining electronic medical records of patients with copperhead snakebites from July 1, 2014 to August 31, 2019. Data collected included: patient demographics, transfer information, snake species, bite site, progression of local tissue effects, additional clinical and lab results, patient comorbidities, and treatment strategy. Associations between patient variables and treatment were evaluated using the chi-square test of independence, median test, and logistic regression analysis. Associations were statistically significant if $p<0.05$. **Discussion:** Of the 130 patients bitten by a copperhead, a majority (75%) received FabAV. Symptoms of copperhead envenomation were mostly limited to the progression of tissue damage. Predictors of treatment with FabAV included progression of venom effects across major joints, younger age, comorbidities, and upper extremity bites. **Conclusions:** Patients who have multiple comorbidities, upper extremity bites and progression of venom effects across major joints are more likely to be treated with FabAV. The high usage of FabAV at the study site underscores the need for continued work to optimize the use of antivenom for copperhead envenomations.