



Réseau MTN Francophone

Veille scientifique Maladies tropicales négligées

Semaine 9

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Dengue, chikungunya et maladie à virus Zika.....	2
Rage	18
Trachome	21
Ulcère de Buruli.....	22
Pian	22
Lèpre	22
Trypanosomes (trypanosomiase et maladie de Chagas)	24
Leishmaniose.....	31
Cysticercose	40
Dracunculose	41
Echinococcose	41
Trématodoses d'origine alimentaire (clonorchiose, opisthorchiase, fasciolase et paragonimose)	44
Filariose lymphatique	46
Mycétome.....	46
Onchocercose	47
Schistosomiase.....	47
Helminthiases transmises par le sol (ascaridiose, trichuriase, ankylostomiase)	51
Gale	52
Morsures de serpent.....	54



DENGUE, CHIKUNGUNYA ET MALADIE A VIRUS ZIKA

Neuroimaging features of arboviral infections in the Americas.

Corrêa, D., Freddi, T., Chaves, C., Hygino da Cruz, L.

01-03-2022

Clin Imaging

<https://pubmed.ncbi.nlm.nih.gov/35247791>

Arboviruses are zoonotic RNA viruses maintained in nature in cycles that involve arthropod vectors. The arboviruses that cause disease in humans are members of the Bunyaviridae, Togaviridae, Flaviviridae, and Reoviridae families. These viral species have geographically and climatically restricted distributions due to particular ecological and vector features. The main emerging arboviruses in the Americas are dengue, zika, yellow fever (Flaviviridae), and chikungunya (Togaviridae). All of these viruses can be transmitted by the *Aedes aegypti* and *Aedes albopictus* mosquitoes. Although not commonly, these infections are associated with neurological complications, characterized mainly by hemorrhage, encephalitis, myelitis, acute disseminated encephalomyelitis, Guillain-Barré syndrome, and/or congenital malformations. This review describes the imaging features of the neurological complications of these emerging arbovirus infections.

Mosquito surveillance and the first record of morphological and molecular-based identification of invasive species *Aedes (Stegomyia) aegypti* (Diptera: Culicidae), southern Iran.

Dorzaban, H., Soltani, A., Alipour, H., Hatami, J., Jaberhashemi, S., Shahriari-Namadi, M., Paksa, A., Safari, R., Talbalaghi, A., Azizi, K.

02-03-2022

Exp Parasitol

<https://pubmed.ncbi.nlm.nih.gov/35247382>

Ae. aegypti is an important vector for transmission of some dangerous arboviral diseases, including Dengue Fever. The present study was conducted (from August 2017 to January 2020) to survey the fauna of Culicine mosquitoes, emphasizing the existence of this invasive species in oriental parts of the country located near the Persian Gulf. Different sampling methods were used to collect all life stages of the mosquito. After morphological identification, a molecular study based on Cytochrome Oxidase (COI) gene-specific primers was performed. Then, the COI gene was sequenced via the Sanger method. A total of 4843 adults and 11,873 larvae were collected (8 species of *Culex*, one species of *Culiseta*, and 5 species of *Aedes*). Fifty-five *Ae. aegypti* specimens (8 adults and 47 larvae) were identified. Based on the biology and ecological requirements of *Ae. aegypti*, the possibility of the permanent establishment of this species in the tropical climate of the region is very likely. Considering the detection of this invasive vector mosquito species in Iran and the high incidence of some

arboviral diseases in the neighboring countries, and continuous movements of the settlers of these areas, potential outbreaks of arboviral diseases can be predicted. Planning and implementing an immediate surveillance and control program of the vector mosquito is vital to prevent the permanent establishment of this invasive vector mosquito species in southern Iran.

Movement dynamics: reduced dengue cases during the COVID-19 pandemic.

Sasmono, R., Santoso, M.

02-03-2022

Lancet Infect Dis

<https://pubmed.ncbi.nlm.nih.gov/35247322>

Measuring the effects of COVID-19-related disruption on dengue transmission in southeast Asia and Latin America: a statistical modelling study.

Chen, Y., Li, N., Lourenço, J., Wang, L., Cazelles, B., Dong, L., Li, B., Liu, Y., Jit, M., Bosse, N., Abbott, S., Velayudhan, R., Wilder-Smith, A., Tian, H., Brady, O., CMMID COVID-19 Working Group

02-03-2022

Lancet Infect Dis

<https://pubmed.ncbi.nlm.nih.gov/35247320>

The COVID-19 pandemic has resulted in unprecedented disruption to society, which indirectly affects infectious disease dynamics. We aimed to assess the effects of COVID-19-related disruption on dengue, a major expanding acute public health threat, in southeast Asia and Latin America. We assembled data on monthly dengue incidence from WHO weekly reports, climatic data from ERA5, and population variables from WorldPop for 23 countries between January, 2014 and December, 2019 and fit a Bayesian regression model to explain and predict seasonal and multi-year dengue cycles. We compared model predictions with reported dengue data January to December, 2020, and assessed if deviations from projected incidence since March, 2020 are associated with specific public health and social measures (from the Oxford Coronavirus Government Response Tracer database) or human movement behaviours (as measured by Google mobility reports). We found a consistent, prolonged decline in dengue incidence across many dengue-endemic regions that began in March, 2020 (2.28 million cases in 2020 vs 4.08 million cases in 2019; a 44.1% decrease). We found a strong association between COVID-19-related disruption (as measured independently by public health and social measures and human movement behaviours) and reduced dengue risk, even after taking into account other drivers of dengue cycles including climatic and host immunity (relative risk 0.01-0.17, $p < 0.01$). Measures related to the closure of schools and reduced time spent in non-residential areas had the strongest evidence of association with reduced dengue risk, but high collinearity between covariates made specific attribution challenging.

Overall, we estimate that 0.72 million (95% CI 0.12-1.47) fewer dengue cases occurred in 2020 potentially attributable to COVID-19-related disruption. In most countries, COVID-19-related disruption led to historically low dengue incidence in 2020. Continuous monitoring of dengue incidence as COVID-19-related restrictions are relaxed will be important and could give new insights into transmission processes and intervention options. National Key Research and Development Program of China and the Medical Research Council.

Cross-species microRNA transmission modulates flavivirus growth in mosquitoes.

Shivaprasad, S., Sarnow, P.

01-03-2022

Trends Parasitol

<https://pubmed.ncbi.nlm.nih.gov/35246384>

Mosquitoes can be infected with a variety of RNA viruses. Recently, Zhu et al. demonstrated that human microRNA hsa-miR-150-5p is acquired by mosquitoes during blood meals and protects the Dengue virus by downregulation of chymotrypsin AaCT-1 mRNA. This finding suggests the use of microRNA antagomirs as an antiviral approach in mosquitoes.

Estimating chikungunya virus transmission parameters and vector control effectiveness highlights key factors to mitigate arboviral disease outbreaks.

Jourdain, F., de Valk, H., Noël, H., Paty, M., L'Ambert, G., Franke, F., Mouly, D., Desenclos, J., Roche, B.

04-03-2022

PLoS Negl Trop Dis

<https://doi.org/10.1371/journal.pntd.0010244>

Viruses transmitted by *Aedes* mosquitoes have greatly expanded their geographic range in recent decades. They are considered emerging public health threats throughout the world, including Europe. Therefore, public health authorities must be prepared by quantifying the potential magnitude of virus transmission and the effectiveness of interventions. We developed a mathematical model with a vector-host structure for chikungunya virus transmission and estimated model parameters from epidemiological data of the two main autochthonous chikungunya virus transmission events that occurred in Southern France, in Montpellier (2014) and in Le Cannet-des-Maures (2017). We then performed simulations of the model using these estimates to forecast the magnitude of the foci of transmission as a function of the response delay and the moment of virus introduction. The results of the different simulations underline the relative importance of each variable and can be useful to stakeholders when designing context-based intervention strategies. The findings emphasize the importance of, and advocate for early detection of imported cases and timely biological confirmation of autochthonous cases to ensure timely vector control measures, supporting the

implementation and the maintenance of sustainable surveillance systems.

Evaluation of insecticide treated window curtains and water container covers for dengue vector control in a large-scale cluster-randomized trial in Venezuela.

Lenhart, A., Castillo, C., Villegas, E., Alexander, N., Vanlerberghe, V., van der Stuyft, P., McCall, P.

04-03-2022

PLoS Negl Trop Dis

<https://doi.org/10.1371/journal.pntd.0010135>

Following earlier trials indicating that their potential in dengue vector control was constrained by housing structure, a large-scale cluster-randomized trial of insecticide treated curtains (ITCs) and water jar covers (ITJCs) was undertaken in Venezuela. In Trujillo, Venezuela, 60 clusters (6223 houses total) were randomized so that 15 clusters each received either PermaNet insecticide-treated window curtains (ITCs), permanent insecticide-treated water storage jar covers (ITJCs), a combination of both ITCs and ITJCs, or no insecticide treated materials (ITMs). A further 15 clusters located at least 5km from the edge of the study site were selected to act as an external control. Entomological surveys were carried out immediately before and after intervention, and then at 6-month intervals over the following 27 months. The Breteau and House indices were used as primary outcome measures and ovitrap indices as secondary. Negative binomial regression models were used to compare cluster-level values of these indices between the trial arms. Reductions in entomological indices followed deployment of all ITMs and throughout the trial, indices in the external control arm remained substantially higher than in the ITM study arms including the internal control. Comparing the ratios of between-arm means to summarise the entomological indices throughout the study, the combined ITC+ITJC intervention had the greatest impact on the indices, with a 63% difference in the pupae per person indices between the ITC+ITJC arm and the internal control. However, coverage had fallen below 60% by 14-months post-intervention and remained below 40% for most of the remaining study period. ITMs can impact dengue vector populations in the long term, particularly when ITCs and ITJCs are deployed in combination. ClinicalTrials.gov ISRCTN08474420; www.isrctn.com.

Global burden and trends of neglected tropical diseases from 1990 to 2019.

Lin, Y., Fang, K., Zheng, Y., Wang, H., Wu, J.

03-03-2022

J Travel Med

<https://pubmed.ncbi.nlm.nih.gov/35238925>

An updated analysis of neglected tropical diseases (NTDs) from a global perspective is missing from the literature. We aimed to assess the global burden and trends of NTDs from 1990 to 2019. Yearly incident case, mortality, and disability-adjusted life years (DALYs) data for NTDs were extracted from the Global

Burden of Disease Study 2019 (GBD 2019) based on global, regional, country, social development index (SDI), age and sex categories. The age-standardized rate (ASR) and number of incident cases, mortality and DALYs were computed from 1990 to 2019. The estimated annual percentage change (EAPC) in the ASR was calculated to quantify the changing trend. Globally, the age-standardized incidence rate (ASIR) and the number of incident cases of total NTDs increased between 1990 and 2019, while the age-standardized mortality rate (ASMR), mortality, age-standardized DALY rate and DALYs of total NTDs decreased. Although tropical Latin America, South Asia, Southeast Asia and Oceania had the highest ASIR for total NTDs in 2019, tropical Latin America was the only region to experience a decreasing trend in ASIR from 1673.5 per 100000 in 2010 to 1059.2 per 100000 in 2019. The middle, high-middle and high SDI regions experienced increasing ASIR trends between 1990 and 2019, while the low-middle SDI region remained stable, and the low SDI region presented a decreasing trend. Children and older adults were vulnerable to dengue, rabies and leishmaniasis (cutaneous and mucocutaneous). Females had a higher ASIR but a lower ASMR and age-standardized DALY rate than males. NTDs still represent a serious problem for public health, and the increasing ASIR and incident cases globally may require more targeted strategies for prevention, control and surveillance, especially among specific populations and endemic areas.

SARS-CoV-2 and dengue virus co-infection: Epidemiology, pathogenesis, diagnosis, treatment, and management.

Prapty, C., Rahmat, R., Araf, Y., Shounak, S., Noor-A-Afrin, ., Rahaman, T., Hosen, M., Zheng, C., Hossain, M.
03-03-2022

Rev Med Virol

<https://doi.org/10.1002/rmv.2340>

SARS-CoV-2 and dengue virus co-infection cases have been on the rise in dengue-endemic regions as coronavirus disease 2019 (COVID-19) spreads over the world, posing a threat of a co-epidemic. The risk of comorbidity in co-infection cases is greater than that of a single viral infection, which is a cause of concern. Although the pathophysiologies of the two infections are different, the viruses have comparable effects within the body, resulting in identical clinical symptoms in the case of co-infection, which adds to the complexity. Overlapping symptoms and laboratory features make proper differentiation of the infections important. However, specific biomarkers provide precise results that can be utilised to diagnose and treat a co-infection, whether it is simply COVID-19, dengue, or a co-infection. Though their treatment is distinguished, it becomes more complicated in circumstances of co-infection. As a result, regardless of whatever infection the first symptom points to, confirmation diagnosis of both COVID-19 and dengue should be mandatory, particularly in dengue-endemic regions, to prevent health deterioration in individuals treated for a single infection. There is still a scarcity of concise literature on the epidemiology, pathophysiology, diagnosis, therapy, and management of SARS-CoV-2 and dengue virus co-infection. The epidemiology of SARS-CoV-2 and dengue virus co-infection, the mechanism of

pathogenesis, and the potential impact on patients are summarised in this review. The possible diagnosis with biomarkers, treatment, and management of the SARS-CoV-2 and dengue viruses are also discussed. This review will shed light on the appropriate diagnosis, treatment, and management of the patients suffering from SARS-CoV-2 and dengue virus co-infection.

In the screening of alternative insecticides to control *Aedes aegypti* larvae 2-methylantraquinone showed no genotoxicity and low toxicity to zebrafish (*Danio rerio*).

Piau, T., Fascineli, M., Moura, D., Albernaz, L., Espindola, L., Grisolia, C.

28-02-2022

Genet Mol Biol

<https://pubmed.ncbi.nlm.nih.gov/35238327>

The threats posed by insecticide resistance to *Aedes aegypti* in the context of controlling dengue have led to an urgent search for an environmentally safer alternative chemical with more effective larvicidal properties. Among many molecules tested, 2-methylantraquinone showed the lowest LC50 for *A. aegypti* in a previous study and the highest LC50 for zebrafish embryos. Embryos were exposed at concentrations of 1.0, 2.19, 4.78, 10.46, 22.87, 50.0 and 100.0 mg/L, and malformations and mortality were significantly observed only at the highest exposures of 50 and 100 mg/L after 96 h. Micronucleus test and comet assay in zebrafish adults were both negative after exposures at 6.25, 12.5, 25.0, 50.0 and 100.0 mg/L for 96 h. Several biochemical biomarkers were analyzed in adults, and 2-methylantraquinone did not interfere with acetylcholinesterase activity. The lactate dehydrogenase activity was higher at concentrations of 25 and 100 mg/L. Glutathione-S-Transferase (GST) activities were tested in the gill and body (muscle tail). The gill was more sensitive than body for GST activity after exposure to 2-methylantraquinone, showing the highest activities, and 2-methylantraquinone showed low toxicity to a non-target organism.

Structures and dynamics of peptide and peptidomimetic inhibitors bound to the NS2B-NS3 protease of the ZIKA virus.

Pant, S., Bhattacharya, G., Jena, N.

03-03-2022

J Biomol Struct Dyn

<https://doi.org/10.1080/07391102.2022.2045223>

Infections caused by the Zika virus (ZIKV) have detrimental effects on human health, in particular on infants. As no potent drug or vaccine is available to date to contain this viral disease, it is necessary to design inhibitors that can target the NS2B-NS3 protease of the ZIKV, which is mainly responsible for the proliferation of the virus inside the host cells. Here, molecular dynamics (MD) simulation and molecular mechanics energies combined with the generalized Born and surface area continuum solvation model (MM/GBSA) are used to

understand the binding modes and stabilities of R, KR, KKR, WKR, WKKR, YKKR, and FKRR peptide inhibitors bound to the NS3-NS2B protease. The results are compared with the corresponding results obtained for covalent (compound **1**) and non-covalent (compound **4***) peptidomimetic inhibitors. It is revealed that peptide inhibitors can bind strongly with the ZIKV protease with the ΔG_{bind} ranging from -12kcal/mol to -73kcal/mol. Among these peptides, YKKR is found to make the most stable complex with the protease and fully occupy the electrostatically active substrate binding site. Hence, it would inhibit the protease activities of ZIKV strongly. The residue-wise decomposition of ΔG_{bind} indicates that Asp75, Asp129, Tyr130, Ser135, Gly151, Asn152, Glu153, and Tyr161 of NS3 and Ser81, Asp83, and Phe84 of NS2B play a prominent role in the inhibitor binding. Therefore, any future design of inhibitors should be aimed to target these residues.

EVITA Dengue: a cluster-randomized controlled trial to Evaluate the efficacy of Wolbachia-Infected Aedes aegypti mosquitoes in reducing the incidence of Arboviral infection in Brazil.

Collins, M., Potter, G., Hitchings, M., Butler, E., Wiles, M., Kennedy, J., Pinto, S., Teixeira, A., Casanovas-Massana, A., Roupheal, N., Deye, G., Simmons, C., Moreira, L., Nogueira, M., Cummings, D., Ko, A., Teixeira, M., Edupuganti, S.
02-03-2022

Trials

<https://doi.org/10.1186/s13063-022-05997-4>

Arboviruses transmitted by *Aedes aegypti* including dengue, Zika, and chikungunya are a major global health problem, with over 2.5 billion at risk for dengue alone. There are no licensed antivirals for these infections, and safe and effective vaccines are not yet widely available. Thus, prevention of arbovirus transmission by vector modification is a novel approach being pursued by multiple researchers. However, the field needs high-quality evidence derived from randomized, controlled trials upon which to base the implementation and maintenance of vector control programs. Here, we report the EVITA Dengue trial design (DMID 17-0111), which assesses the efficacy in decreasing arbovirus transmission of an innovative approach developed by the World Mosquito Program for vector modification of *Aedes* mosquitoes by *Wolbachia pipiensis*. DMID 17-0111 is a cluster-randomized trial in Belo Horizonte, Brazil, with clusters defined by primary school catchment areas. Clusters ($n = 58$) will be randomized 1:1 to intervention (release of *Wolbachia*-infected *Aedes aegypti* mosquitoes) vs. control (no release). Standard vector control activities (i.e., insecticides and education campaigns for reduction of mosquito breeding sites) will continue as per current practice in the municipality. Participants ($n = 3480$, 60 per cluster) are children aged 6-11 years enrolled in the cluster-defining school and living within the cluster boundaries who will undergo annual serologic surveillance for arboviral infection. The primary objective is to compare sero-incidence of arboviral infection between arms. DMID 17-0111 aims to determine the efficacy of *Wolbachia*-infected mosquito releases in reducing human infections by arboviruses transmitted by *Aedes aegypti* and will complement

the mounting evidence for this method from large-scale field releases and ongoing trials. The trial also represents a critical step towards robustness and rigor for how vector control methods are assessed, including the simultaneous measurement and correlation of entomologic and epidemiologic outcomes. Data from this trial will inform further the development of novel vector control methods. ClinicalTrials.gov NCT04514107. Registered on 17 August 2020. Primary sponsor: National Institute of Health, National Institute of Allergy and Infectious Diseases.

Melatonin attenuates dimethyl sulfoxide- and Zika virus-induced degeneration of porcine induced neural stem cells.

Horcharoensuk, P., Yang-En, S., Chakritbudsabong, W., Samatiwat, P., Pramong, R., Rungarunlert, S., Rungsiwirut, R.

02-03-2022

In Vitro Cell Dev Biol Anim

<https://doi.org/10.1007/s11626-022-00648-z>

Domestic pigs have become increasingly popular as a model for human diseases such as neurological diseases. Drug discovery platforms have increasingly been used to identify novel compounds that combat neurodegeneration. Currently, bioactive molecules such as melatonin have been demonstrated to offer a neuroprotective effect in several studies. However, a neurodegenerative platform to study novel compounds in a porcine model has not been fully established. In this study, characterized porcine induced neural stem cells (iNSCs) were used for evaluation of the protective effect of melatonin against chemical and pathogenic stimulation. First, the effects of different concentrations of melatonin on the proliferation of porcine iNSCs were studied. Second, porcine iNSCs were treated with the appropriate concentration of melatonin prior to induced degeneration with dimethyl sulfoxide or Zika virus (ZIKV). The results demonstrated that the percentages of Ki67 expression in porcine iNSCs cultured in 0.1, 1, and 10 nM melatonin were not significantly different from that in the control groups. Melatonin at 1 nM protected porcine iNSCs from DMSO-induced degeneration, as confirmed by a dead cell exclusion assay and mitochondrial membrane potential ($\Delta\Psi_m$) analysis. In addition, pretreatment with melatonin reduced the percentage of dead porcine iNSCs after ZIKV infection. Melatonin increased the $\Delta\Psi_m$, resulting in a decrease in cell degeneration. However, pretreatment with melatonin was unable to suppress ZIKV replication in porcine iNSCs. In conclusion, the present study demonstrated the anti-degenerative effect of melatonin against DMSO- and ZIKV-induced degeneration in porcine iNSCs.

The interaction of dengue virus capsid protein with negatively charged interfaces drives the in vitro assembly of nucleocapsid-like particles.

Mebus-Antunes, N., Ferreira, W., Barbosa, G., Neves-Martins, T., Weissmuller, G., Almeida, F., Da Poian, A.

01-03-2022

PLoS One

<https://doi.org/10.1371/journal.pone.0264643>

Dengue virus (DENV) causes a major arthropod-borne viral disease, with 2.5 billion people living in risk areas. DENV consists in a 50 nm-diameter enveloped particle in which the surface proteins are arranged with icosahedral symmetry, while information about nucleocapsid (NC) structural organization is lacking. DENV NC is composed of the viral genome, a positive-sense single-stranded RNA, packaged by the capsid (C) protein. Here, we established the conditions for a reproducible in vitro assembly of DENV nucleocapsid-like particles (NCLPs) using recombinant DENVC. We analyzed NCLP formation in the absence or presence of oligonucleotides in solution using small angle X-ray scattering, Rayleigh light scattering as well as fluorescence anisotropy, and characterized particle structural properties using atomic force and transmission electron microscopy imaging. The experiments in solution comparing 2-, 5- and 25-mer oligonucleotides established that 2-mer is too small and 5-mer is sufficient for the formation of NCLPs. The assembly process was concentration-dependent and showed a saturation profile, with a stoichiometry of 1:1 (DENVC:oligonucleotide) molar ratio, suggesting an equilibrium involving DENVC dimer and an organized structure compatible with NCLPs. Imaging methods proved that the decrease in concentration to sub-nanomolar concentrations of DENVC allows the formation of regular spherical NCLPs after protein deposition on mica or carbon surfaces, in the presence as well as in the absence of oligonucleotides, in this latter case being surface driven. Altogether, the results suggest that in vitro assembly of DENV NCLPs depends on DENVC charge neutralization, which must be a very coordinated process to avoid unspecific aggregation. Our hypothesis is that a specific highly positive spot in DENVC $\alpha 4-\alpha 4'$ is the main DENVC-RNA binding site, which is required to be firstly neutralized to allow NC formation.

Long-term Chikungunya sequelae and quality of life 2.5 years post-acute disease in a prospective cohort in Curaçao.

Doran, C., Elsinga, J., Fokkema, A., Berenschot, K., Gerstenbluth, I., Duits, A., Lourents, N., Halabi, Y., Burgerhof, J., Bailey, A., Tami, A.

01-03-2022

PLoS Negl Trop Dis

<https://doi.org/10.1371/journal.pntd.0010142>

Little is known about the persistence and impact of non-rheumatic symptoms after acute chikungunya disease. We have studied the clinical presentation and long-term impact of rheumatic and non-rheumatic symptoms on health related quality of life (QoL) 2.5 years after disease onset. Additionally, the validity of the Curaçao Long-Term Chikungunya Sequelae (CLTCS) score in classifying disease severity over time was evaluated. This prospective cohort study followed 248 chikungunya patients. Symptoms and SF-36 QoL were evaluated during baseline and follow-up at 2.5 years using questionnaires. Chikungunya disease status was classified using

the CLTCS-score. At 2.5 years after disease onset patients were classified as being recovered (43%), mildly (35%) or highly (22%) affected. In comparison to mildly affected, highly affected patients reported the highest prevalence of ongoing rheumatic and non-rheumatic/psychological symptoms, with increased prevalence of arthralgia in the lower extremities ($p = .01$) and fatigue ($p = .049$) over time, and higher pain intensity ($p < .001$). Compared to mildly affected, being highly affected was associated with weakness in the lower extremities (OR: 1.90; CI: 1.29-2.80, $p = .001$) and worsened physical and mental QoL impairment. Patients are both physically and psychologically affected by rheumatic and non-rheumatic symptoms of long-term chikungunya disease. The CLTCS-score is an easy to use instrument for classifying long-term chikungunya disease severity and impact and can facilitate health care providers in identifying highly affected patients who are prone to develop severe QoL impairment. Highly affected patients are recommended to be treated in a multidisciplinary setting to improve physical and psychological functioning, and QoL.

Recent Progress in Graphene- and Related Carbon-Nanomaterial-based Electrochemical Biosensors for Early Disease Detection.

Fahmy, H., Abu Serea, E., Salah-Eldin, R., Al-Hafiry, S., Ali, M., Shalan, A., Lanceros-Méndez, S.

01-03-2022

ACS Biomater Sci Eng

<https://doi.org/10.1021/acsbiomaterials.1c00710>

Graphene- and carbon-based nanomaterials are key materials to develop advanced biosensors for the sensitive detection of many biomarkers owing to their unique properties. Biosensors have attracted increasing interest because they allow efficacious, sensitive, selective, rapid, and low-cost diagnosis. Biosensors are analytical devices based on receptors for the process of detection and transducers for response measuring. Biosensors can be based on electrochemical, piezoelectric, thermal, and optical transduction mechanisms. Early virus identification provides critical information about potentially effective and selective therapies, extends the therapeutic window, and thereby reduces morbidity. The sensitivity and selectivity of graphene can be amended via functionalizing it or conjoining it with further materials. Amendment of the optical and electrical features of the hybrid structure by introducing appropriate functional groups or counterparts is especially appealing for quick and easy-to-use virus detection. Various techniques for the electrochemical detection of viruses depending on antigen-antibody interactions or DNA hybridization are discussed in this work, and the reasons behind using graphene and related carbon nanomaterials for the fabrication are presented and discussed. We review the existing state-of-the-art directions of graphene-based classifications for detecting DNA, protein, and hormone biomarkers and summarize the use of the different biosensors to detect several diseases, like cancer, Alzheimer's disease, and diabetes, to sense numerous viruses, including SARS-CoV-2, human immunodeficiency virus, rotavirus, Zika virus, and hepatitis B

virus, and to detect the recent pandemic virus COVID-19. The general concepts, mechanisms of action, benefits, and disadvantages of advanced virus biosensors are discussed to afford beneficial evidence of the creation and manufacture of innovative virus biosensors. We emphasize that graphene-based nanomaterials are ideal candidates for electrochemical biosensor engineering due to their special and tunable physicochemical properties.

Zika virus congenital microcephaly severity classification and the association of severity with neuropsychomotor development.

Esper, N., Franco, A., Soder, R., Bomfim, R., Nunes, M., Radaelli, G., Esper, K., Kotoski, A., Pripp, W., Neto, F., Azambuja, L., Mathias, N., da Costa, D., Portugez, M., da Costa, J., Buchweitz, A.

01-03-2022

Pediatr Radiol

<https://doi.org/10.1007/s00247-022-05284-z>

Zika virus infection during pregnancy is linked to birth defects, most notably microcephaly, which is associated with neurodevelopmental delays. The goals of the study were to propose a method for severity classification of congenital microcephaly based on neuroradiologic findings of MRI scans, and to investigate the association of severity with neuropsychomotor developmental scores. We also propose a semi-automated method for MRI-based severity classification of microcephaly. We conducted a cross-sectional investigation of 42 infants born with congenital Zika infection. Bayley Scales of Infant and Toddler Development III (Bayley-III) developmental evaluations and MRI scans were carried out at ages 13-39 months (mean: 24.8 months; standard deviation [SD]: 5.8 months). The severity score was generated based on neuroradiologist evaluations of brain malformations. Next, we established a distribution of Zika virus-microcephaly severity score including mild, moderate and severe and investigated the association of severity with neuropsychomotor developmental scores. Finally, we propose a simplified semi-automated procedure for estimating the severity score based only on volumetric measures. The results showed a correlation of $r=0.89$ ($P<0.001$) between the Zika virus-microcephaly severity score and the semi-automated method. The trimester of infection did not correlate with the semi-automated method. Neuropsychomotor development correlated with the severity classification based on the radiologic readings and semi-automated method; the more severe the imaging scores, the lower the neuropsychomotor developmental scores. These severity classification methods can be used to evaluate severity of microcephaly and possible association with developmental consequences. The semi-automated methods thus provide an alternative for predicting severity of microcephaly based on only one MRI sequence.

Population-based assessment of factors influencing antibiotic prescribing for adults with dengue infection in Taiwan.

Lien, C., Chou, Y., Shen, Y., Tsai, T., Huang, N.

28-02-2022

PLoS Negl Trop Dis

<https://doi.org/10.1371/journal.pntd.0010198>

Antibiotic treatment for dengue is likely considerable and potentially avoidable but has not been well characterized. This study aimed to assess antibiotic prescribing for confirmed dengue cases in outpatient and inpatient settings and to identify associated patient, physician and contextual factors. 57,301 adult dengue cases reported in Taiwan between 2008-2015 were analyzed. We assessed both outpatient and inpatient claims data of dengue patients from a week before to a week after their dengue infections were confirmed under Taiwan's National Health Insurance program. A multivariable logistic regression with generalized estimating equations was used to estimate the probability of antibiotic prescribing in dengue patients. Overall, 24.6% of dengue patients were prescribed an antibiotic during the 14 day-assessment period. Antibiotics were prescribed in 6.1% and 30.1% of outpatient visits and inpatient admissions, respectively. Antibiotic prescriptions were reduced by ~50% in epidemic years. Among inpatients, advanced age, females, and major comorbidities were risk factors for receipt of an antibiotic; antibiotics were used in 26.0% of inpatients after dengue was diagnosed. Significant differences in antibiotic prescribing practices were observed among physicians in outpatient settings but not in inpatient settings. In addition to patient and physician demographic characteristics, contextual factors such as care setting and during epidemics significantly influenced prescription of antibiotics. Characterization of prescribing patterns should help direct programs to curb antibiotic prescribing.

Assessment of the clinical and laboratorial profile of patients with obesity and asymptomatic COVID-19 undergoing bariatric surgery in Brazil.

Santa-Cruz, F., Araújo-Júnior, J., Siqueira, L., Leão, L., Vianna, C., Almeida, A., Silva, M., Kreimer, F., Ferraz, Á.

28-02-2022

Obes Surg

<https://doi.org/10.1007/s11695-022-05891-7>

to outline the clinical and laboratorial profile of patients with obesity undergoing bariatric surgery who presented positive reverse transcription-polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome coronavirus-2 (Sars-CoV-2) in the preoperative period without symptoms presentation. Case series of 17 patients undergoing bariatric surgery who presented positive RT-PCR for Sars-CoV-2 in the preoperative period, with no reported symptoms. Data collected included demographic characteristics, length of hospital stay, waiting time for surgery, inflammatory markers, serum levels of micronutrients and dengue virus (DENV) serology. In total, 219 patients underwent bariatric surgery in our institution during the study period. The incidence of asymptomatic cases was 7.7%. The sample comprised 88.2% of women, with mean age of 39.3 years and mean preoperative body mass index (BMI) of

37.7 kg/m². Thirty five percent of the sample had previous diagnosis of diabetes and 29.4% had hypertension. The mean time elapsed between positive RT-PCR and the operation was 17±7.5 days and the mean length of postoperative hospital stay was 1.9±0.43 day. Mean lymphocytes count was 2,409.7/mm³ and the mean platelet-to-lymphocyte ratio was 126.3. Mean C-reactive protein value was 5.8 mg/dL, while ferritin marked 107.4 µg/L. DENV IgG was identified in all patients who tested for it. Mean levels of vitamin D and zinc were 25.6 ng/mL and 79.9 µg/dL, respectively. There were no postoperative complications reported. None of the included patients presented any of the laboratory markers related to disease severity. Moreover, it is important to notice that all patients who tested for DENV, had the specific IgG detected in their serum.

Commentary: Evidence of dengue virus in eviscerated specimens of panophthalmitis secondary to dengue fever: A possible cause-effect phenomenon.

Mahendradas, P., Sanjay, S., Kawali, A., Mishra, S., Shetty, B.

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Indian J Ophthalmol

https://doi.org/10.4103/ijo.IJO_2604_21

Evidence of dengue virus in eviscerated specimens of panophthalmitis secondary to dengue fever: A possible cause-effect phenomenon.

Dave, T., Sharma, S., Lakshmi, V., Rangaihgari, A., Murthy, S., Ali, M., Dave, V., Pappuru, R.

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Indian J Ophthalmol

https://doi.org/10.4103/ijo.IJO_1732_21

To report a retrospective series of three cases of infectious panophthalmitis post-dengue fever with ex vivo confirmation of dengue virusribonucleic acid (RNA) in the tissues of the eye. Four eyes of three patients, who were diagnosed with panophthalmitis following dengue fever and who underwent evisceration, were included. All demographic and clinical data were recorded. The eviscerated samples were subjected to direct microscopy, culture for bacteria, fungi, and parasites, and molecular virology (dengue virus [DENV] NS1-specific reverse transcription loop-mediated isothermal amplification (RT-LAMP) assay). The time from the development of dengue fever to the occurrence of ocular symptoms was 4.33 ± 1.15 (median 5) days. DENV NS1 RNA, suggestive of the presence of the dengue virus, was confirmed in all evisceration specimens (uveal tissue, cornea). All the patients recovered completely from dengue fever and on follow-up had healthy eviscerated sockets. Demonstration of the DENV RNA in the eviscerated specimens of panophthalmitis following dengue fever implicates the DENV in the pathophysiology of the ocular infection.

Mathematical models for dengue fever epidemiology: A 10-year systematic review.

Aguiar, M., Anam, V., Blyuss, K., Estadilla, C., Guerrero, B., Knopoff, D., Kooi, B., Srivastav, A., Steindorf, V., Stollenwerk, N.

15-02-2022

Phys Life Rev

<https://pubmed.ncbi.nlm.nih.gov/35219611>

Mathematical models have a long history in epidemiological research, and as the COVID-19 pandemic progressed, research on mathematical modeling became imperative and very influential to understand the epidemiological dynamics of disease spreading. Mathematical models describing dengue fever epidemiological dynamics are found back from 1970. Dengue fever is a viral mosquito-borne infection caused by four antigenically related but distinct serotypes (DENV-1 to DENV-4). With 2.5 billion people at risk of acquiring the infection, it is a major international public health concern. Although most of the cases are asymptomatic or mild, the disease immunological response is complex, with severe disease linked to the antibody-dependent enhancement (ADE) - a disease augmentation phenomenon where pre-existing antibodies to previous dengue infection do not neutralize but rather enhance the new infection. Here, we present a 10-year systematic review on mathematical models for dengue fever epidemiology. Specifically, we review multi-strain frameworks describing host-to-host and vector-host transmission models and within-host models describing viral replication and the respective immune response. Following a detailed literature search in standard scientific databases, different mathematical models in terms of their scope, analytical approach and structural form, including model validation and parameter estimation using empirical data, are described and analyzed. Aiming to identify a consensus on infectious diseases modeling aspects that can contribute to public health authorities for disease control, we revise the current understanding of epidemiological and immunological factors influencing the transmission dynamics of dengue. This review provide insights on general features to be considered to model aspects of real-world public health problems, such as the current epidemiological scenario we are living in.

Molecular tweezers - a new class of potent broad-spectrum antivirals against enveloped viruses.

Le, M., Taghuo K, E., Schrader, T.

01-03-2022

Chem Commun (Camb)

<https://doi.org/10.1039/d1cc06737k>

A new supramolecular approach to broad spectrum antivirals utilizes host guest chemistry between molecular tweezers and lysine/arginine as well as choline. Basic amino acids in amyloid-forming SEVI peptides (semen-derived enhancers of viral infection) are included inside the tweezer cavity leading to disaggregation and neutralization of the fibrils, which lose their ability to enhance HIV-1/HIV-2 infection. Lipid head groups contain the trimethylammonium cation of choline; this is

likewise bound by molecular tweezers, which dock onto viral membranes and thus greatly enhance their surface tension. Disruption of the envelope in turn leads to total loss of infectivity (ZIKA, Ebola, Influenza). This complexation event also seems to be the structural basis for an effective inhibition of cell-to-cell spread in Herpes viruses. The article describes the discovery of novel molecular recognition motifs and the development of powerful antiviral agents based on these host guest systems. It explains the general underlying mechanisms of antiviral action and points to future optimization and application as therapeutic agents.

Current status and perspectives on vaccine development against dengue virus infection.

Park, J., Kim, J., Jang, Y.

14-02-2022

J Microbiol

<https://doi.org/10.1007/s12275-022-1625-y>

Dengue virus (DENV) consists of four serotypes in the family Flaviviridae and is a causative agent of dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. DENV is transmitted by mosquitoes, *Aedes aegypti* and *A. albopictus*, and is mainly observed in areas where vector mosquitoes live. The number of dengue cases reported by the World Health Organization increased more than 8-fold over the last two decades from 505,430 in 2000 to over 2.4 million in 2010 to 5.2 million in 2019. Although vaccine is the most effective method against DENV, only one commercialized vaccine exists, and it cannot be administered to children under 9 years of age. Currently, many researchers are working to resolve the various problems hindering the development of effective dengue vaccines; understanding of the viral antigen configuration would provide insight into the development of effective vaccines against DENV infection. In this review, the current status and perspectives on effective vaccine development for DENV are examined. In addition, a plausible direction for effective vaccine development against DENV is suggested.

Spontaneous globe rupture: Unusual ophthalmic manifestation with dengue hemorrhagic shock syndrome.

Kaur, R., Singh, H., Sehgal, A., Singh, J.

23-01-2022

Am J Ophthalmol Case Rep

<https://doi.org/10.1016/j.ajoc.2022.101297>

We report an unusual manifestation of spontaneous globe rupture in a 9 year old male child with dengue hemorrhagic shock syndrome. Nine year old male was admitted in the pediatric intensive care unit in a state of altered sensorium secondary to dengue hemorrhagic shock syndrome. Ophthalmic examination revealed proptosis and hemorrhagic chemosis of the right eye. Within two hours of presentation, spontaneous globe rupture with extrusion of intraocular contents occurred in spite of aggressive treatment and intravenous methylprednisolone. Spontaneous globe rupture

in a child with dengue hemorrhagic shock syndrome with such a rapid course is being reported for the first time in literature. Ophthalmologists and pediatricians should be alert regarding vision threatening manifestations related to dengue hemorrhagic shock syndrome.

Early Predictors of Poor Neurologic Outcomes in a Prospective Cohort of Infants With Antenatal Exposure to Zika Virus.

Tiene, S., Cranston, J., Nielsen-Saines, K., Kerin, T., Fuller, T., Vasconcelos, Z., Marschik, P., Zhang, D., Pone, M., Pone, S., Zin, A., Brickley, E., Orofino, D., Brasil, P., Adachi, K., da Costa, A., Lopes Moreira, M.

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Pediatr Infect Dis J

<https://doi.org/10.1097/INF.0000000000003379>

Identify early predictors of poor neurodevelopment in infants with antenatal Zika virus (ZIKV) exposure. Analysis of a prospective cohort of infants with antenatal ZIKV exposure confirmed by maternal or infant RT-PCR or IgM during the epidemic in Rio de Janeiro, Brazil. Clinical findings before 3 months of age were associated with Bayley-III Scales of Infant and Toddler Development conducted after 6 months of age. ZIKV exposure was confirmed in 219 cases; 162 infants were normocephalic, 53 were microcephalic, 4 had no head circumference recorded because of perinatal death/LTFU. Seven of the 112 normocephalic infants developed secondary microcephaly between 3 weeks and 8 months of age. Among the normocephalic at birth cohort, the mean HCZ among normal, at risk, and developmentally delayed children was significantly different (ANOVA, $P=0.02$). In particular, the mean HCZ of the developmentally delayed group was significantly lower than that of the normal group (Tukey's test, $P=0.014$). HCZ was more strongly associated with lower expressive language scores ($P=0.04$) than receptive language scores ($P=0.06$). The rate of auditory abnormalities differed among the normal, at risk, and developmentally delayed groups (Chi-squared test, $P=0.016$), which was driven by the significant difference between the normal and at risk groups (post hoc test, $P=0.011$, risk ratio 3.94). Auditory abnormalities were associated with both expressive and receptive language delays ($P=0.02$ and $P=0.02$, respectively). Clear predictors of neurodevelopment in normocephalic ZIKV-exposed children have not been previously identified. Our findings demonstrate that smaller HCZ and auditory abnormalities in these infants correlate with poor neurodevelopment as toddlers. Language delay is the most prominent developmental concern among these children, who will require frequent auditory and speech evaluations throughout childhood.

Antiviral effects of azithromycin: A narrative review.

Khoshnood, S., Shirani, M., Dalir, A., Moradi, M., Haddadi, M., Sadeghifard, N., Birjandi, F., Yashmi, I., Heidary, M.

04-02-2022

Biomed Pharmacother

<https://pubmed.ncbi.nlm.nih.gov/35131658>

Viral infections have a great impact on human health. The urgent need to find a cure against different viruses led us to investigations in a vast range of drugs. Azithromycin (AZT), classified as a macrolide, showed various effects on different known viruses such as severe acute respiratory syndrome coronavirus (SARS-CoV), Zika, Ebola, Enterovirus (EVs) and Rhinoviruses (RVs), and Influenza A previously; namely, these viruses, which caused global concerns, are considered as targets for AZT different actions. Due to AZT background in the treatment of known viral infections mentioned above (which is described in this study), in the early stages of COVID-19 (a new zoonotic disease caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) development, AZT drew attention to itself due to its antiviral and immunomodulatory effects as a valuable candidate for COVID-19 treatment. AZT usage instructions for treating different viral infections have always been under observation, and COVID-19 is no exception. There are still debates about the use of AZT in COVID-19 treatment. However, eventually, novel researches convinced WHO to announce the discontinuation of AZT use (alone or in combination with hydroxychloroquine) in treating SARS-CoV-2 infection. This research aims to study the structure of all of the viruses mentioned above and the molecular and clinical effects of AZT against the virus.

Characterization of an Allosteric Pocket in Zika Virus NS2B-NS3 Protease.

Santos, N., Santos, L., Torquato Quezado de Magalhães, M., Lei, J., Hilgenfeld, R., Salgado Ferreira, R., Bleicher, L.
07-02-2022

J Chem Inf Model

<https://doi.org/10.1021/acs.jcim.1c01326>

The NS2B-NS3 protease from Zika virus (ZIKV NS2B-NS3pro) cleaves the viral polyprotein, being essential for its replication and a therapeutic target. Inhibitors that target the active site of ZIKV NS2B-NS3pro have been developed, but they tend to have unfavorable pharmacokinetic properties due to their highly positive charge. Thus, the characterization of allosteric sites in this protease provides new strategies for inhibitor development. Here, we characterized a new allosteric pocket in ZIKV NS2B-NS3pro, analogous to the one previously described for the dengue virus protease. Molecular dynamics simulations indicate the presence of cavities around the residue Ala125, sampling protein conformations in which they are connected to the active site. This link between the residue Ala125 and the active site residues was reinforced by correlation network analysis. To experimentally verify the existence of this allosteric mechanism, we expressed and purified the Ala125Cys mutant of ZIKV NS2B-NS3pro and demonstrated that this variant is inhibited by the thiol-containing chemical probes 5,5'-dithiobis-(2-nitrobenzoic acid) and aldrithiol, which do not affect the activity of the wild-type protein. Inhibition of the mutant protein is reversed by the addition of strong reducing agents, supporting the involvement of Cys125 in covalent bond formation and enzyme inhibition. Together, our results provide

experimental evidence for an allosteric pocket in ZIKV NS2B-NS3pro, in the region around Ala125, and computational insights on the structural connection between this region and the enzyme active site.

SAR evolution towards potent C-terminal carboxamide peptide inhibitors of Zika virus NS2B-NS3 protease.

Colarusso, S., Ferrigno, F., Ponzi, S., Pavone, F., Conte, I., Abate, L., Beghetto, E., Missineo, A., Amaudrut, J., Bresciani, A., Paonessa, G., Tomei, L., Montalbetti, C., Bianchi, E., Toniatti, C., Ontoria, J.

23-01-2022

Bioorg Med Chem

<https://pubmed.ncbi.nlm.nih.gov/35123179>

Zika virus (ZIKV) is a member of the Flaviviridae family that can cause neurological disorders and congenital malformations. The NS2B-NS3 viral serine protease is an attractive target for the development of new antiviral agents against ZIKV. We report here a SAR study on a series of substrate-like linear tripeptides that inhibit in a non-covalent manner the NS2B-NS3 protease. Optimization of the residues at positions P1, P2, P3 and of the N-terminal and C-terminal portions of the tripeptide allowed the identification of inhibitors with sub-micromolar potency with phenylglycine as arginine-mimicking group and benzylamide as C-terminal fragment. Further SAR exploration and application of these structural changes to a series of peptides having a 4-substituted phenylglycine residue at the P1 position led to potent compounds showing double digit nanomolar inhibition of the Zika protease ($IC_{50} = 30$ nM) with high selectivity against trypsin-like proteases and the proteases of other flavivirus, such as Dengue 2 virus (DEN2V) and West Nile virus (WNV).

Detection of Zika RNA virus in *Aedes aegypti* and *Aedes albopictus* mosquitoes, São Paulo, Brazil.

Parra, M., Lorenz, C., de Aguiar Milhim, B., Dibo, M., Guirado, M., Chiaravalloti-Neto, F., Nogueira, M.

25-01-2022

Infect Genet Evol

<https://pubmed.ncbi.nlm.nih.gov/35085788>

We conducted mosquito-based Zika virus surveillance in São Paulo State, Brazil from 2015 to 2018. We found 81 pools positive for *Aedes aegypti* and one pool positive for *Aedes albopictus*. Infection rates were highest in the summer. Areas with human Zika cases also had clusters of Zika-positive mosquitoes.

A flavivirus-inducible gene expression system that modulates broad-spectrum antiviral activity against dengue and Zika viruses.

Weng, S., Zhou, Y., Shiao, S.

21-01-2022

Insect Biochem Mol Biol

<https://pubmed.ncbi.nlm.nih.gov/35074522>

Incidence of dengue virus (DENV) and Zika virus (ZIKV), two mosquito-borne flaviviruses, is increasing in large parts of the world. Vaccination and medication for these diseases are unsatisfactory. Here, we developed a novel antiviral approach, using a virus-inducible gene expression system, to block virus replication and transmission. Constructs containing the smallest replication units of dengue virus serotype 2 (DENV2) with negative-stranded DENV2 artificial genomes and genes of interest were established in an *Aedes aegypti* cell line, resulting in expression of target genes after DENV2 infection. Green fluorescent protein (GFP) assays confirmed the system was virus-inducible. When we used one of two apoptosis-related genes, *A. aegypti* michelob_x (AaMx) and inhibitor of apoptosis (IAP)-antagonist michelob_x-like protein (AaIMP) instead of GFP, the production of viral RNA and proteins were inhibited for all five viruses tested (DENV1-4 and ZIKV), and effector caspase activity was induced. The system thus inhibited the production of infectious virus particles *in vitro*, and in mosquitoes it did so after DENV2 infection. This is a novel broad-spectrum antiviral approach using a flavivirus-inducible gene-expression system, which could lead to new avenues for mosquito-borne disease control.

Integrated view of molecular diagnosis and prognosis of dengue viral infection: future prospect of exosomes biomarkers.

Rana, R., Kant, R., Kaul, D., Sachdev, A., Ganguly, N.

21-01-2022

Mol Cell Biochem

<https://doi.org/10.1007/s11010-021-04326-8>

Dengue viruses (DENVs) are the viruses responsible for dengue infection which affects lungs, liver, heart and also other organs of individuals. DENVs consist of the group of four serotypically diverse dengue viruses transmitted in tropical and sub-tropical countries of world. *Aedes* mosquito is the principal vector which spread the infection from infected person to healthy humans. DENVs can cause different syndromes depending on serotype of virus which range from undifferentiated mild fever to dengue hemorrhagic fever resulting in vascular leakage due to release of cytokine and Dengue shock syndrome with fluid loss and hypotensive shock, or other severe manifestations such as bleeding and organ failure. Increase in dengue cases in pediatric population is a major concern. Transmission of dengue depends on various factors like temperature, rainfall, and distribution of *Aedes aegypti* mosquitoes. The present review describes a comprehensive overview of dengue, pathophysiology, diagnosis, treatment with an emphasis on potential of exosomes as biomarkers for early prediction of dengue in pediatrics.

Acute macular neuroretinopathy in dengue virus serotype 1.

Guardiola, G., Villegas, V., Cruz-Villegas, V., Schwartz, S.

03-01-2022

Am J Ophthalmol Case Rep

<https://doi.org/10.1016/j.ajoc.2021.101250>

To report a case of acute macular neuroretinopathy (AMN) associated with dengue virus serotype 1 infection. An 18-year-old Puerto Rican female was evaluated due to painless paracentral scotomas in each eye that developed after being hospitalized for dengue fever a week before. Clinical examination and multimodal imaging revealed bilateral hypopigmented macular lesions, hyperreflectivity at the outer nuclear and photoreceptor layer, and reduced flow signal in the deep capillary plexus. Additionally, hypoautofluorescent parafoveal lesions were found in the left eye. AMN was diagnosed. Two-month follow-up after the initial evaluation showed resolution of symptoms but persistence of some findings on optical coherence tomography. Patients with dengue virus serotype 1 may develop paracentral scotomas with classic AMN findings and obtain complete symptomatic recovery without treatment.

Differential detection of zika virus based on PCR.

Alzate, D., Marín, E., Orozco, J., Muskus, C.

07-01-2022

J Virol Methods

<https://pubmed.ncbi.nlm.nih.gov/35007627>

Tropical countries are highly prone to infectious diseases such as the one caused by zika virus. Infection by zika is clinically and epidemiologically highly relevant. For example, when women are infected by zika during the first trimester of pregnancy, the child incurs a high risk of microcephaly and acute neurological syndromes. In adults, the virus is associated with the Guillain-Barré syndrome and other disorders. The worldwide emergency caused by zika in 2013/14 demonstrated the need for rapid and accurate diagnostic tools for the virus. Current diagnostic methods include virus isolation, serological tests, and molecular assays. However, virus isolation requires labor-intensive and time-consuming cell culture; serological detection suffers from cross-reactivity caused by previous exposure to homologous arboviruses that cause symptoms like those caused by zika, while molecular tools commonly are not designed for differential zika detection. This work reports on developing a specific molecular detection method based on phylogenetically conserved primers designed for the specific diagnosis of the zika virus. The zika primers were systematically selected through a rigorous bioinformatic analysis and demonstrated the capability to be highly specific. We tested our primers on synthetic DNA, cell cultures and samples from patients infected with zika, dengue and chikungunya and found that they detected zika with specificity high enough for differential virus diagnosis.

New insights into the recombinant proteins and monoclonal antibodies employed to immunodiagnosis and control of Zika virus infection: A review.

Magalhães, I., Souza, P., Marques, L., Girão, N., Araújo, F., Guedes, M.

05-01-2022

Int J Biol Macromol

<https://pubmed.ncbi.nlm.nih.gov/34998869>

An emergent positive-stranded RNA virus, transmitted by mosquitoes with its first case of vertical transmission confirmed in 2015 in Brazil. The Zika virus (ZIKV) fever has received particular attention, mainly related to neurological diseases such as microcephaly in newborns. However, the laboratory diagnosis for ZIKV still faces some challenges due to its cross-reactivity with other flaviviruses, requiring a correct and differential diagnosis, contributing to the good prognosis of patients, especially in pregnant women. Among these, for early diagnosis, the CDC considers the RT-PCR the gold standard, more sensitive and specific, but expensive. Serological tests for the diagnosis of ZIKV can also be found beyond the period when the viral components are detectable in the serum. Inputs to produce more sensitive and specific diagnostic kits and the possibility of viral detection in less invasive samples are among the objectives of recent research on ZIKV. This review outlines recent advances in developing recombinant antigen and antibody-based diagnostic tools for the main flaviviruses in Northeast Brazil, such as ZIKV and Dengue virus (DENV).

Activating receptor KIR2DS2 bound to HLA-C1 reveals the novel recognition features of activating receptor.

Yang, Y., Bai, H., Wu, Y., Chen, P., Zhou, J., Lei, J., Ye, X., Brown, A., Zhou, X., Shu, T., Chen, Y., Wei, P., Yin, L.

11-01-2022

Immunology

<https://doi.org/10.1111/imm.13439>

Killer cell immunoglobulin-like receptors (KIRs) are important receptors for regulating the killing of virus-infected or cancer cells of natural killer (NK) cells. KIR2DS2 can recognize peptides derived from hepatitis C virus (HCV) or global flaviviruses (such as dengue and Zika) presented by HLA-C*0102 to activate NK cells, and has shown promising results when used for cancer immunotherapy. Here, we present the complex structure of KIR2DS2 with HLA-C*0102 at a resolution of 2.5 Å. Our structure reveals that KIR2DS2 can bind with HLA-C*0102 and HLA-A*1101 in two different directions. Moreover, Tyr45 (in activating receptor KIR2DS2) and Phe45 (in inhibitory KIRs) distinguish the two different binding models and binding affinity between activating KIRs and inhibitory KIRs. The conserved 'AT' motif of the peptide mediates recognition and determines the peptide specificity of recognition. These structural characteristics shed light on how KIRs activate NK cells and can provide a molecular basis for immunotherapy by NK cells.

Synthesis and Anti-dengue Virus Activity of 5-Ethynylimidazole-4-carboxamide (EICA) Nucleotide Prodrugs.

Nakamura, M., Uemura, K., Saito-Tarashima, N., Sato, A., Orba, Y., Sawa, H., Matsuda, A., Maenaka, K., Minakawa, N.

25-12-2021

Chem Pharm Bull (Tokyo)

<https://doi.org/10.1248/cpb.c21-01038>

We previously showed that 5-ethynyl-(1-β-D-ribofuranosyl)imidazole-4-carboxamide (1; EICAR) is a potent anti-dengue virus (DENV) compound but is cytotoxic to some cell lines, while its 4-thio derivative, 5-ethynyl-(4-thio-1-β-D-ribofuranosyl)imidazole-4-carboxamide (2; 4'-thioEICAR), has less cytotoxicity but also less anti-DENV activity. Based on the hypothesis that the lower anti-DENV activity of 2 is due to reduced susceptibility to phosphorylation by cellular kinase(s), we investigated whether a monophosphate prodrug of 2 can improve its activity. Here, we first prepared two types of prodrug of 1, which revealed that the S-acyl-2-thioethyl (SATE) prodrug had stronger anti-DENV activity than the aryloxyphosphoramidate (so-called ProTide) prodrug. Based on these findings, we next prepared the SATE prodrug of 4'-thioEICAR 18. As expected, the resulting 18 showed potent anti-DENV activity, which was comparable to that of 1; however, its cytotoxicity was also increased relative to 2. Our findings suggest that prodrugs of 4'-thioribonucleoside derivatives such as EICAR (1) represent an effective approach to developing potent biologically active compounds; however, the balance between antiviral activity and cytotoxicity remains to be addressed.

G-quadruplex microspheres-based optical RNA biosensor for arthropod-borne virus pathogen detection: A proof-of-concept with dengue serotype 2.

Jamaluddin, N., Mazlan, N., Tan, L., Yusof, N., Khalid, B.

16-12-2021

Int J Biol Macromol

<https://pubmed.ncbi.nlm.nih.gov/34922999>

Dengue virus (DENV) is a positive-sense single-stranded RNA virus and that the detection of viral RNA itself is highly desirable, which can be achieved by using RNA biosensor diagnostic method. Herein, acrylic micropolymer-based optical RNA biosensor was developed by binding anionic copper(II) phthalocyanine (CPC) planar aromatic ligand to the G-quadruplex DNA probe via end-stacking with π-system of the guanine (G) quartet, and a blue coloration was developed on the G-quadruplex microspheres. Hybridization of G-quadruplex DNA probe with target DENV serotype 2 (DENV2) RNA unfolded the G-quadruplex, and rendering release of the CPC planar optical label, causing discoloration of the G-quadruplex microbiosensor. Optical characterization of the RNA biosensor was performed by means of fiber optic reflectance spectrophotometer at maximum reflectance wavelength of 774 nm. The reflectance response enhancement of the RNA-responsive G-quadruplex-based reflectometric biosensor was linearly proportional to the target oligo DENV2 RNA concentration in the range of 2 zM-2 μM, with a 0.447 zM limit of detection and a rapid response time of 30 min. Heightening

in the reflectance signal based on structural transition of G-quadruplex in response to target RNA was successfully implemented in real-time DENV2 detection in non-invasive human fluid samples (i.e. saliva and urine) under informed consent.

Vaccination for Dengue Prevention.

Adams, L., Waterman, S., Paz-Bailey, G.

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JAMA

<https://doi.org/10.1001/jama.2021.23466>

Correction to: Salidroside exhibits anti-dengue virus activity by upregulating host innate immune factors.

Sharma, N., Mishra, K., Ganju, L.

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Arch Virol

<https://doi.org/10.1007/s00705-021-05321-6>

Mortality Rates of Severe Dengue Viral Infection Before and After Implementation of a Revised Guideline for Severe Dengue.

Laoprasopwattana, K., Khantee, P., Saelim, K., Geater, A.

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Pediatr Infect Dis J

<https://doi.org/10.1097/INF.0000000000003411>

To compare the mortality rate of severe dengue (SD) before and after implementation of a revised SD guideline. Medical records of SD patients <15 years of age hospitalized during 1998-2020 were reviewed. The revised SD guidelines were implemented in 2016, including intensive monitoring of vital signs and intra-abdominal pressure, the release of intra-abdominal pressure in cases of abdominal compartment syndrome (ACS) and the use of N-acetyl cysteine in cases of acute liver failure. On initial admission, organ failure including severe bleeding, acute respiratory failure, acute kidney injury and acute liver failure was not significantly different between 78 and 23 patients treated in the pre- and postrevised guideline periods, respectively. After hospitalization, the proportions of patients who developed profound shock (68.8% vs. 41.2%), multiorgan failures (60.4% vs. 73.3%), ACS (37.2% vs. 26.1%) and fatal outcome (33.3% vs. 13.0%) were also not significantly different between the pre- and postrevised guideline periods, respectively. In subgroup analysis, the mortality rates in patients with multiorgan failure (44.1% vs. 15.8%), acute respiratory failure and active bleeding (78.1% vs. 37.5%) and ACS (82.8% vs. 33.3%), respectively, were significantly higher in the pre- than the postrevised guideline periods. The durations of time before the liver function tests returned to normal levels, and the mortality rates in acute liver failure patients treated with and without N-acetyl cysteine were not significantly different. Although following the revised guidelines could not prevent organ failure, the mortality rates in patients with

multiorgan failure and/or ACS decreased significantly when following the revised guidelines.

Chikungunya, Zika, Mayaro, and Equine Encephalitis virus detection in adult Culicinae from South Central Mato Grosso, Brazil, during the rainy season of 2018.

da Silva Neves, N., da Silva Ferreira, R., Morais, D., Pavon, J., de Pinho, J., Shlessarenko, R.

17-11-2021

Braz J Microbiol

<https://doi.org/10.1007/s42770-021-00646-5>

Several arboviruses causing human disease have been reported in Brazil. In nature, arboviruses maintain a lifecycle involving vertebrates and vectors, which may contribute for periodical reemergence of those of public health concern in tropical regions, as Mato Grosso State (MT). In this study, we searched for arboviruses in mosquito body pools sampled during the rainy season of 2018 in 21 bird watching points of Cuiabá and Varzea Grande, South Central MT. In total, 2873 (57%) males and 2167 (43%) females belonging to six urban and sylvatic mosquito genera allocated to 398 pools were subjected to RNA extraction and RT-PCR for arboviruses. Positive pools were subjected to virus isolation in C6/36 cells. A total of 102/398 pools, 66/233 (29.6%) of females, and 36/165 (21.8%) of males, mostly sampled in May (31/102), were positive for arboviruses. Chikungunya virus (CHIKV) was distributed in 19 points, Zika virus (ZIKV) was found in 14 points, Mayaro virus (MAYV) in 10 points, and East Equine encephalitis virus (EEEV) in three points. *Culex quinquefasciatus* pools (39/89 of females and 24/99 of males) were positive for CHIKV, ZIKV, and MAYV; *Aedes (Stg) aegypti* pools (11/46 of females and 12/33 of males) for CHIKV, ZIKV, MAYV, and EEEV; *Aedes albopictus* female pools (8/29) for CHIKV, ZIKV, and EEEV; and *Psorophora albigena* (2/12) and *Psorophora ferox* female pools (4/16) for CHIKV. Arbovirus molecular detection in mosquito populations varies considerable between geographical regions and epidemics, influenced by genetic characteristics and microbiome interference on virus replication. Although infected females are responsible for the transmission to vertebrates during bloodfeeding, male infection by CHIKV, ZIKV, and MAYV resultant from vertical route could lead to interepidemic maintenance of these arboviruses in their natural reservoirs.

Analysis of influenza and dengue cases in Mexico before and during the COVID-19 pandemic.

Cruz-Lopez, F., Garza-González, E., Morfin-Otero, R., Villarreal-Treviño, L., Rodríguez-Noriega, E., Martínez-Meléndez, A.

09-11-2021

Infect Dis (Lond)

<https://doi.org/10.1080/23744235.2021.1999496>

Economic evaluation of Zika Contraception Access Network in Puerto Rico during the 2016-17 Zika virus outbreak.

Li, R., Ellington, S., Galang, R., Grosse, S., Mendoza, Z., Hurst, S., Vale, Y., Lathrop, E., Romero, L.

05-11-2021

Contraception

<https://pubmed.ncbi.nlm.nih.gov/34748752>

During the 2016-2017 Zika virus (ZIKV) outbreak, the prevention of unintended pregnancies was identified as a primary strategy to prevent birth defects. This study estimated the cost-effectiveness of the Zika Contraception Access Network (Z-CAN), an emergency response intervention that provided women in Puerto Rico with access to the full range of reversible contraception at no cost and compared results with a preimplementation hypothetical cost-effectiveness analysis (CEA). We evaluated costs and outcomes of Z-CAN from a health sector perspective compared to no intervention using a decision tree model. Number of people served, contraception methods mix, and costs under Z-CAN were from actual program data and other input parameters were from the literature. Health outcome measures included the number of Zika-associated microcephaly (ZAM) cases and unintended pregnancies. The economic benefits of the Z-CAN intervention were ZIKV-associated direct costs avoided, including lifetime medical and supportive costs associated with ZAM cases, costs of monitoring ZIKV-exposed pregnancies and infants born from Zika-virus infected mothers, and the costs of unintended pregnancies prevented during the outbreak as a result of increased contraception use through the Z-CAN intervention. The Z-CAN intervention cost a total of \$26.1 million, including costs for the full range of reversible contraceptive methods, contraception related services, and programmatic activities. The program is estimated to have prevented 85% of cases of estimated ZAM cases and unintended pregnancies in the absence of Z-CAN. The intervention cost was projected to have been more than offset by \$79.9 million in ZIKV-associated costs avoided, 96% of which were lifetime ZAM-associated costs, as well as \$137.0 million from avoided unintended pregnancies, with total net savings in one year of \$216.9 million. The results were consistent with the previous CEA study. Z-CAN was likely cost-saving in the context of a public health emergency response setting.

Identification of potential new mosquito-associated viruses of adult *Aedes aegypti* mosquitoes from Tocantins state, Brazil.

Duarte, M., Campos, F., Araújo Neto, O., Silva, L., Silva, A., Aguiar, T., Santos, R., Souza, U., Alves, G., Melo, F., Ardisson-Araujo, D., Aguiar, R., Ribeiro, B.

02-11-2021

Braz J Microbiol

<https://doi.org/10.1007/s42770-021-00632-x>

Medically important arboviruses such as dengue virus (DENV), Zika virus (ZIKV), and chikungunya virus (CHIKV) are primarily transmitted by the globally distributed mosquito *Aedes aegypti*.

Increasing evidence suggests that the transmission of some viruses can be influenced by mosquito-specific and mosquito-borne viruses. Advancements in high-throughput sequencing (HTS) and bioinformatics have expanded our knowledge on the richness of viruses harbored by mosquitoes. HTS was used to characterize the presence of virus sequences in wild-caught adult *Ae. aegypti* from Tocantins (TO) state, Brazil. Samples of mosquitoes were collected in four cities of Tocantins state and submitted to RNA isolation, followed by sequencing at an Illumina HiSeq platform. Our results showed initially by Krona the presence of 3% of the sequenced reads belonging to the viral database. After further analysis, the virus sequences were found to have homology to two viral families found in insects Phenuiviridae and Metaviridae. Three possible viral strains including putative new viruses were detected and named Phasi Charoen-like phasivirus isolate To-1 (PCLV To-1), *Aedes aegypti* To virus 1 (AAToV1), and *Aedes aegypti* To virus 2 (AAToV2). The results presented in this work contribute to the growing knowledge about the diversity of viruses in mosquitoes and might be useful for future studies on the interaction between insect-specific viruses and arboviruses.

Comparison of two rapid test kits with real time polymerase chain reaction for early diagnosis of dengue in Sri Lanka.

Ariyaratne, M., Gunasekara, P., Wajirasena, P., Rathnayake, D., Dilani, D., Chathuranga, T., Gomes, L., Jayatunga, D., Wewita, S., Meegahage, T., Jayasinghearachchi, H., Wijewickrama, A., Malavige, G., De Silva, A.

02-11-2021

J Immunoassay Immunochem

<https://doi.org/10.1080/15321819.2021.1984252>

Dengue is among the deadliest insect-borne diseases circulating in Sri Lanka. Most of the infections that are diagnosed early are manageable. However, delays in diagnosis may cause fatalities. We evaluated the dengue NS1 antigen card and NS1 SD kit for early diagnosis of dengue using samples from 116 RT-PCR-positive patients admitted within 5 days of the fever onset. RT-PCR tests were performed as standard tests. IgM and IgG ELISA tests were carried out to identify primary and secondary infections. Of the 116 patients who tested positive for dengue using PCR, 48 were positive using NS1 antigen card and 45 were positive using NS1 SD. Patients with 100 copies or higher viral load showed a higher sensitivity in both antigen card and NS1 SD. Of 34 primary infections evaluated, 23 were positive by NS1 antigen card, while the positivity was 21 by NS1 SD. Of the 30 secondary infections evaluated, 15 were positive by NS1 antigen card while 14 by NS1 SD. Our findings showed that while the rapid tests are convenient and much easier to use than PCR, they are less sensitive and need improvement. Until then, clinical diagnosis should have more emphasis on the early diagnosis of dengue.

Two-year follow-up of children with congenital Zika syndrome: the evolution of clinical patterns.

Rua, E., de Oliveira, S., de Oliveira Vianna, R., Dalcastel, L., de Castro Sarmet Dos Santos, T., Cardoso, C., Fernandes, A.
18-10-2021

Eur J Pediatr

<https://doi.org/10.1007/s00431-021-04280-z>

The aim of the study was to describe neurological manifestations in children with congenital Zika syndrome (CZS) in the first 2 years of age. In this prospective observational study, children with CZS treated at a university hospital received a neurological assessment and were evaluated using two neurodevelopmental scales (the Denver II test and the assessment of gross motor development of the World Health Organization) by a pediatric neurologist on admission to the study and at 4, 8, 12, 18, and 24 months of age. The data collected were stored in Microsoft Excel version 14.6.3. Thirty-eight children (27 males and 11 females; a median age of 4.3 months (interquartile range (IQR): 1.6-11.4)) with CZS were evaluated. Irritability was present in 50% and 27% of the children at 8 months and 24 months, respectively. Axial hypertonia was highly prevalent at 4 months (77%), with a decrease to 50% at 24 months. At all ages, spastic tetraparesis was the most common motor abnormality (>80%). Twenty-seven (71%) participants were diagnosed with epilepsy, and the median age at seizure onset was 6 months (IQR: 3.5-8). The most frequent types of seizures were focal seizures and spasms, with spasms being the most frequent in the first year of life (52%) and focal crises being the most frequent in the second year of life (50%). Conclusion: This study allowed observation of neurological abnormalities over time, the evolution of epileptic manifestations, and recognition of new patterns of clinical neurological abnormalities, helping clinicians to recognize CZS earlier, minimizing the impact of new outbreaks. What is Known: • Clinical patterns of SZC patients at pre-established ages or date of data collection • More frequent studies with data collection of clinical-radiological features of patient's over his first year of life What is New: • Comprehensive clinical neurological progression data regarding CZS in the first 2 years of life, recognizing patterns • Hypothesis including a new CZS spectrum with milder clinical-radiological features.

Larvicidal and repellent activity of N-methyl-1-adamantylamine and oleic acid a major derivative of bael tree ethanol leaf extracts against dengue mosquito vector and their biosafety on natural predator.

Chellappandian, M., Senthil-Nathan, S., Karthi, S., Vasantha-Srinivasan, P., Kalaivani, K., Hunter, W., Ali, A., Veerabahu, C., Elshikh, M., Al Farraj, D.

11-10-2021

Environ Sci Pollut Res Int

<https://doi.org/10.1007/s11356-021-16219-w>

Aegle marmelos (L.) Correa belongs to the family Rutaceae is generally known as "bael fruit tree" occurring across the south Asian countries. The current investigation screened the main derivatives from crude ethanolic extracts of the Bael tree leaf

and evaluated activity effects on the larvae and adults of *Aedes aegypti* (L.) Dengue vector mosquito and a non-target aquatic predator. The GC-MS results showed that the peak area was found to be profound in N-methyl-1-adamantaneacetamide (N-M 1a) followed by oleic acid (OA) with 63.08 and 11.43% respectively. The larvicidal activity against the fourth instar larvae and the crude Ex-Am showed prominent mortality rate (93.60%) at the maximum dosage of 100 ppm. The mortality rate of N-M 1a and OA was occurred at 10 ppm (97.73%) and 12 ppm (95.4%). The repellent activity was found to be prominent at crude Ex-Am (50 ppm) as compared to the pure compounds (N-m 1a and OA) with maximum protection time up to 210 min. The non-target screening of Ex-Am, N-M 1a, and OA on mosquito predator *Tx. splendens* showed that they are scarcely toxic even at the maximum dosage of 1000 ppm (34.13%), 100 ppm (27.3%), and 120 ppm (31.3%) respectively. Thus, the present investigation clearly proved that the crude Ex-Am and their major derivatives Nm 1-a and OA showed their acute larval toxicity as well as potential mosquito repellent against the dengue mosquito and eco-safety against the mosquito predator.

Oviposition dynamics of *Aedes aegypti* in Central Argentina.

Sánchez-Díaz, E., Gleiser, R., Lopez, L., Guzman, C., Contigiani, M., Spinsanti, L., Gardenal, C., Gorla, D.

07-10-2021

Med Vet Entomol

<https://doi.org/10.1111/mve.12550>

Aedes (*Stegomyia*) *aegypti* (L.) (Diptera: Culicidae) is the vector of multiple arboviruses. To evaluate the association between environmental factors and the oviposition activity of *Ae. aegypti* in Argentina, data on the presence and abundance of eggs were collected using ovitraps, between September of 2018 and May of 2019, in the cities of Villa María, Río Cuarto and Salsipuedes (Córdoba province, Argentina). We analysed the relationships between oviposition and five environmental factors: Temperature, precipitation, vegetation cover, human population density and distance to sites with a potential high density of larval habitats, like cemeteries and trash dumps. Environmental factors' data were collected using satellite image products. The oviposition activity was randomly distributed in three cities. Using generalized linear mixed models, we show that the house where each ovitrap was placed was a source of variability in oviposition, suggesting the relevance of microsite factors and the importance of domestic control actions. *Ae. aegypti* oviposition was positively correlated with night-time temperature of the previous 3 weeks, and in a context-dependent manner, it was positively correlated with human population density, vegetation cover and precipitation. The consistency and magnitude of these relationships varied between cities, indicating that oviposition is related to a complex system of environmental variables.

PANoptosis in Viral Infection: The Missing Puzzle Piece in the Cell Death Field.

Nguyen, L., Kanneganti, T.

16-09-2021

J Mol Biol

<https://pubmed.ncbi.nlm.nih.gov/34537233>

In the past decade, emerging viral outbreaks like SARS-CoV-2, Zika and Ebola have presented major challenges to the global health system. Viruses are unique pathogens in that they fully rely on the host cell to complete their lifecycle and potentiate disease. Therefore, programmed cell death (PCD), a key component of the host innate immune response, is an effective strategy for the host cell to curb viral spread. The most well-established PCD pathways, pyroptosis, apoptosis and necroptosis, can be activated in response to viruses. Recently, extensive crosstalk between PCD pathways has been identified, and there is evidence that molecules from all three PCD pathways can be activated during virus infection. These findings have led to the emergence of the concept of PANoptosis, defined as an inflammatory PCD pathway regulated by the PANoptosome complex with key features of pyroptosis, apoptosis, and/or necroptosis that cannot be accounted for by any of these three PCD pathways alone. While PCD is important to eliminate infected cells, many viruses are equipped to hijack host PCD pathways to benefit their own propagation and subvert host defense, and PCD can also lead to the production of inflammatory cytokines and inflammation. Therefore, PANoptosis induced by viral infection contributes to either host defense or viral pathogenesis in context-specific ways. In this review, we will discuss the multi-faceted roles of PCD pathways in controlling viral infections.

A switch-on molecular biosensor for detection of caspase-3 and imaging of apoptosis of cells.

Gong, R., Wang, D., Abbas, G., Li, S., Liu, Q., Cui, M., Zhang, X.

09-09-2021

Sci China Life Sci

<https://doi.org/10.1007/s11427-021-1986-7>

Apoptosis is a form of programmed cell death that is essential for maintaining internal environmental stability. Disordered apoptosis can cause a variety of diseases; therefore, sensing apoptosis can provide help in study of mechanism of the relevant diseases and drug development. It is known that caspase-3 is a key enzyme involved in apoptosis and the expression of its activity is an indication of apoptosis. Here, we present a genetically encoded switch-on mNeonGreen2-based molecular biosensor. mNeonGreen2 is the brightest monomeric green fluorescent protein. The substrate of caspase-3, DEVD amino acid residues, is inserted in it, while cyclized by insertion of Nostoc punctiforme DnaE intein to abolish the fluorescence (inactive state). Caspase-3-catalyzed cleavage of DEVD linearizes mNeonGreen2 and rebuilds the natural barrel structure to restore the fluorescence (activated state). The characterization exhibited that the Caspase-3 biosensor has shortened response time, higher sensitivity, and prolonged functional shelf life in detection of caspase-3 amongst the existing counterparts. We also used the Caspase-

3 biosensor to evaluate the effect of several drugs on the induction of apoptosis of HeLa and MCF-7 tumor cells and inhibition of Zika virus invasion.

Neurodevelopment in normocephalic children with and without prenatal Zika virus exposure.

Blackmon, K., Evans, R., Fernandes, M., Landon, B., Noel, T., Macpherson, C., Cudjoe, N., Burgen, K., Punch, B., Krystosik, A., Grossi-Soyster, E., LaBeaud, A., Waechter, R.

03-09-2021

Arch Dis Child

<https://doi.org/10.1136/archdischild-2020-321031>

Zika virus (ZIKV) targets neural stem cells in the developing brain. However, the majority of ZIKV-exposed children are born without apparent neurological manifestations. It remains unclear if these children were protected from ZIKV neurotropism or if they harbour subtle pathology that is disruptive to brain development. We assess this by comparing neurodevelopmental outcomes in normocephalic ZIKV-exposed children relative to a parallel control group of unexposed controls. Cohort study. Public health centres in Grenada, West Indies. 384 mother-child pairs were enrolled during a period of active ZIKV transmission (April 2016-March 2017) and prospectively followed up to 30 months. Child exposure status was based on laboratory assessment of prenatal and postnatal maternal serum. The INTERGROWTH-21st Neurodevelopment Assessment (INTER-NDA) package and Cardiff Vision Tests, administered and scored by research staff masked to child's exposure status. A total of 131 normocephalic ZIKV exposed (n=68) and unexposed (n=63) children were assessed between 22 and 30 months of age. Approximately half of these children completed vision testing. There were no group differences in sociodemographics. Deficits in visual acuity (31%) and contrast sensitivity (23%) were apparent in the ZIKV-exposed infants in the absence of cognitive, motor, language or behavioural delays. Overall neurodevelopment is likely to be unaffected in ZIKV-exposed children with normal head circumference at birth and normal head growth in the first 2 years of life. However, the visual system may be selectively vulnerable, which indicates the need for vision testing by 3 years of age.

Correlation of serotype-specific strain in patients with dengue virus infection with neurological manifestations and its outcome.

Pandey, A., Verma, R., Jain, A., Prakash, S., Garg, R., Malhotra, H., Sharma, P., Kumar, N., Uniyal, R., Pandey, S., Rizvi, I.

02-08-2021

Neurol Sci

<https://doi.org/10.1007/s10072-021-05477-8>

Neurological manifestation of dengue virus infection is a rare entity. Serotypes commonly associated with neurological manifestation are DENV-2 and DENV-3. We plan to detect the serotypes related to the neurological presentation in dengue

infection and its correlation with different neurological complications and outcome. In this case-control study, consecutive dengue cases with different neurological manifestations were enrolled along with age and sex-matched controls (dengue patients without neurological complication). Serotyping using RT-PCR of samples of cases and controls were done. Level of correlation was analyzed with various parameters and outcomes. In cases out of 33 samples, 6 sample serotypes were detected, which were composed of DENV-1 (n=2) and DENV-2 (n=4). In controls, DENV-1 (n=5), DENV-2 (n=6), and DENV-3 (n=3) were detected. When statistically correlated, no significant association was found in cases and controls with dengue virus serotype. The frequency of serotype 2 was higher in hypokalemic paralysis cases than non-hypokalemic paralysis cases and the difference was significant ($p < 0.05$). The outcome was good (mRS < 3) in all the cases where serotypes were detected, but on statistical correlation, it was not found significant ($p > 0.05$). DENV-1 and DENV-2 are associated with neurological manifestation of dengue infection, which is different from the existing literature, where DENV-2 and DENV-3 are reported. The detection of DENV serotype will help in predicting and best management of neurological complication. The serotype 2 of dengue virus is more commonly associated with dengue-associated hypokalemic paralysis than other neurological complication ($p < 0.05$). There is no significant association of serotypes with outcome or mortality.

Seroprevalence estimate and risk factors for *Coxiella burnetii* infections among humans in a highly urbanised Brazilian state.

Meurer, I., Silva, M., Silva, M., de Lima Duré, A., Adelino, T., da Costa, A., Vanelli, C., de Paula Souza E Guimarães, R., Rozental, T., de Lemos, E., Corrêa, J.

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Trans R Soc Trop Med Hyg

<https://doi.org/10.1093/trstmh/trab113>

Q fever is among the top 13 global priority zoonoses, however, it is still neglected and under-reported in most of the world, including Brazil. Thus, we evaluated the seroprevalence of and the risk factors for *Coxiella burnetii* infections in humans from Minas Gerais, a highly urbanised Brazilian state. *Coxiella burnetii* was searched for patient samples (n=437), which were suspected of then later confirmed as negative for dengue fever, by the indirect immunofluorescence technique and real-time PCR. Risk factors for infections and spatial clusters for both *C. burnetii*-seropositive individuals and livestock concentration were evaluated. We found that 21 samples (4.8%; 95% CI 3.0 to 7.2%) were reactive for at least one class of anti-*C. burnetii* antibodies (titer of ≥ 64), with rural residence ($p = 0.036$) being a risk factor. Also, two spatial clusters of seropositivity were found within a significant area by Scan, and a probable relationship between the Scan result and the livestock concentration by area was found. Seropositive individuals were associated with rural residence, with a likely relationship with the livestock concentration. Thus, this study establishes baseline figures for *C. burnetii* seroprevalence in humans in a

state of Brazil, allowing the monitoring of trends and setting of control targets, as well as more representative longitudinal and risk analysis studies.

Dengue virus infection induces inflammation and oxidative stress on the heart.

Kangussu, L., Costa, V., Olivon, V., Queiroz-Junior, C., Gondim, A., Melo, M., Reis, D., Nóbrega, N., Araújo, N., Rachid, M., Souza, R., Tirapelli, C., Santos, R., Cruz, J., Teixeira, M., Souza, D., Bonaventura, D.

28-05-2021

Heart

<https://doi.org/10.1136/heartjnl-2020-318912>

Dengue fever is one of the most important arboviral diseases in the world, and its severe forms are characterised by a broad spectrum of systemic and cardiovascular hallmarks. However, much remains to be elucidated regarding the pathogenesis triggered by *Dengue virus* (DENV) in the heart. Herein, we evaluated the cardiac outcomes unleashed by DENV infection and the possible mechanisms associated with these effects. A model of an adapted DENV-3 strain was used to infect male BALB/c mice to assess haemodynamic measurements and the functional, electrophysiological, inflammatory and oxidative parameters in the heart. DENV-3 infection resulted in increased systemic inflammation and vascular permeability with consequent reduction of systolic blood pressure and increase in heart rate. These changes were accompanied by a decrease in the cardiac output and stroke volume, with a reduction trend in the left ventricular end-systolic and end-diastolic diameters and volumes. Also, there was a reduction trend in the calcium current density in the ventricular cardiomyocytes of DENV-3 infected mice. Indeed, DENV-3 infection led to leucocyte infiltration and production of inflammatory mediators in the heart, causing pericarditis and myocarditis. Moreover, increased reactive oxygen species generation and lipoperoxidation were also verified in the cardiac tissue of DENV-3 infected mice. DENV-3 infection induced a marked cardiac dysfunction, which may be associated with inflammation, oxidative stress and electrophysiological changes in the heart. These findings provide new cardiac insights into the mechanisms involved in the pathogenesis triggered by DENV, contributing to the research of new therapeutic targets for clinical practice.

Access to Contraceptive Services in Puerto Rico: An Analysis of Policy and Practice Change Strategies, 2015-2018.

Romero, L., Corrada-Rivera, R., Huertas-Pagan, X., Aquino-Serrano, F., Morales-Boscio, A., Sanchez-Cesareo, M., Acosta-Perez, E., Mendoza, Z., Lathrop, E.

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J Public Health Manag Pract

<https://doi.org/10.1097/PHH.0000000000001342>

During the 2016-2017 Zika virus outbreak in Puerto Rico, preventing unintended pregnancy was a primary strategy to

reduce Zika-related adverse birth outcomes. The Zika Contraception Access Network (Z-CAN) was a short-term emergency response intervention that used contraception to prevent unintended pregnancy among women who chose to delay or avoid pregnancy. This analysis reports on the identified policy and practice change strategies to increase access to or provision of contraceptive services in Puerto Rico between 2015 and 2018. A policy review was conducted to document federal- and territorial-level programs with contraceptive coverage and payment policies in Puerto Rico and to identify policy and practice change. Semistructured interviews with key stakeholders in Puerto Rico were also conducted to understand perceptions of policy and practice change efforts following the Zika virus outbreak, including emergency response, local, and policy efforts to improve contraception access in Puerto Rico. Publicly available information on federal and territorial programs with policies that facilitate access, delivery, and utilization of contraceptive coverage and family planning services in Puerto Rico to support contraceptive access was documented; however, interview results indicated that the implementation of the policies was often limited by barriers and that policy and practice changes as the result of the Zika virus outbreak were short-term. Consideration of long-term policy and practice changes related to contraceptive access is warranted. Similar analyses can be used to identify policies, practices, and perceptions in other settings in which the goal is to increase access to contraception or reduce unintended pregnancy.

Designed thiazolidines: an arsenal for the inhibition of nsP3 of CHIKV using molecular docking and MD simulations.

Meena, M., Kumar, D., Jayaraj, A., Kumar, A., Kumari, K., Katata-Seru, L., Bahadur, I., Kumar, V., Sherawat, A., Singh, P.

19-10-2020

J Biomol Struct Dyn

<https://doi.org/10.1080/07391102.2020.1832918>

Chikungunya virus (CHIKV) belongs to the alpha virus and its infection in humans causes fever, known as chikungunya fever (CHIKF). It is a sudden onset of fever and may affect humans badly. The mode of transmission to human occurs due to the biting of the mosquitoes. Till date, thousands of humans are affected from this virus throughout the world. As on date, no promising medicine or vaccine is available in the market to cure from this viral infection. Therefore, there is a need of promising candidate against the nsP3 of CHIKV. In the present work, a library of the compounds are designed based on the product obtained in a multi-component reaction. Then, the designed compounds are filtered based on binding energy against the nsP3 of CHIKV obtained using molecular docking. Further, to understand the interaction of nsP3 of CHIKV and screened compound, CMPD474, the molecular dynamics (MD) simulations at different temperatures, that is, 300, 325, 350, 375, and 400K is performed. The binding or the formation of the complex is studied through different trajectories obtained from MD simulations. The accurate information for the binding

energy is determined by performing MM-GBSA calculations and the best inhibition was observed at 300K as the change in free energy for the formation of the complex is -7.0523 kcal/mol. Communicated by Ramaswamy H. Sarma.

RAGE

Mapping thalamic-anterior cingulate monosynaptic inputs in adult mice.

Xue, M., Shi, W., Zhou, S., Li, Y., Wu, F., Chen, Q., Liu, R., Zhou, Z., Zhang, Y., Chen, Y., Xu, F., Bi, G., Li, X., Lu, J., Zhuo, M.

03-03-2022

Mol Pain

<https://doi.org/10.1177/17448069221087034>

The anterior cingulate cortex (ACC) is located in the frontal part of the cingulate cortex, and plays important roles on pain perception and emotion. The thalamocortical pathway is the major sensory input to the ACC. Previous studies show that several different thalamic nuclei receive projection fibers from spinothalamic tract, that in turn send efferents to the ACC by using neural tracers and optical imaging methods. Most of these studies were performed in monkeys, cats and rats, few studies were reported systematically in adult mice. Adult mice, especially genetically modified mice, have provided molecular and synaptic mechanisms for cortical plasticity and modulation in the ACC. In the present study, we utilized rabies virus-based retrograde tracing system to map thalamic-anterior cingulate monosynaptic inputs in adult mice. We also combined with a new high-throughput VISoR imaging technique to generate a three-dimensional whole-brain reconstruction, especially the thalamus. We found that cortical neurons in the ACC received direct projections from different subnuclei in the thalamus, including the anterior, ventral, medial, lateral, midline and intralaminar thalamic nuclei. These findings provide key anatomic evidences for the connection between the thalamus and ACC.

From dogs to bats: Concerns regarding vampire bat-borne rabies in Brazil.

Horta, M., Ledesma, L., Moura, W., Lemos, E.

03-03-2022

PLoS Negl Trop Dis

<https://doi.org/10.1371/journal.pntd.0010160>

Global burden and trends of neglected tropical diseases from 1990 to 2019.

Lin, Y., Fang, K., Zheng, Y., Wang, H., Wu, J.

03-03-2022

J Travel Med

<https://pubmed.ncbi.nlm.nih.gov/35238925>

An updated analysis of neglected tropical diseases (NTDs) from a global perspective is missing from the literature. We aimed to assess the global burden and trends of NTDs from 1990 to 2019. Yearly incident case, mortality, and disability-adjusted life years (DALYs) data for NTDs were extracted from the Global Burden of Disease Study 2019 (GBD 2019) based on global, regional, country, social development index (SDI), age and sex categories. The age-standardized rate (ASR) and number of incident cases, mortality and DALYs were computed from 1990 to 2019. The estimated annual percentage change (EAPC) in the ASR was calculated to quantify the changing trend. Globally, the age-standardized incidence rate (ASIR) and the number of incident cases of total NTDs increased between 1990 and 2019, while the age-standardized mortality rate (ASMR), mortality, age-standardized DALY rate and DALYs of total NTDs decreased. Although tropical Latin America, South Asia, Southeast Asia and Oceania had the highest ASIR for total NTDs in 2019, tropical Latin America was the only region to experience a decreasing trend in ASIR from 1673.5 per 100000 in 2010 to 1059.2 per 100000 in 2019. The middle, high-middle and high SDI regions experienced increasing ASIR trends between 1990 and 2019, while the low-middle SDI region remained stable, and the low SDI region presented a decreasing trend. Children and older adults were vulnerable to dengue, rabies and leishmaniasis (cutaneous and mucocutaneous). Females had a higher ASIR but a lower ASMR and age-standardized DALY rate than males. NTDs still represent a serious problem for public health, and the increasing ASIR and incident cases globally may require more targeted strategies for prevention, control and surveillance, especially among specific populations and endemic areas.

Two-year immunogenicity of a pre-exposure rabies vaccination administered as a two-dose schedule.

Windels, L., Naneix-Laroche, V., Pasquier, C., Delobel, P., Parize, P., Martin-Blondel, G.

02-03-2022

J Travel Med

<https://pubmed.ncbi.nlm.nih.gov/35238924>

In a young and healthy population, immunogenicity at two years of a rabies PrEP in a two-dose IM schedule is satisfying. This regimen may be appropriate in people occupationally exposed to RABV, or traveling to highly endemic countries, provided they receive two booster doses in case of exposure.

lncRNA EDAL restricts rabies lyssavirus replication in a cell-specific and infection route-dependent manner.

Sui, B., Zhao, J., Zheng, J., Zhou, M., Chen, H., Fu, Z., Zhao, L.

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J Gen Virol

<https://doi.org/10.1099/jgv.0.001725>

Rabies, caused by rabies lyssavirus (RABV), is a fatal disease among humans and almost all warm-blooded animals. Our previous study showed that the long non-coding RNA (lncRNA) EZH2 degradation-associated lncRNA (EDAL) effectively inhibits

RABV infection both *in vitro* and *in vivo* by degrading EZH2 and promoting the transcription of an antiviral gene, *Pcp411*. Herein, we found that recombinant RABV expressing EDAL (rRABV-EDAL) restricts RABV replication in primary granule neurons but not in primary cortical neurons or astrocytes. Further study revealed that EDAL induced EZH2 protein degradation and thereby decreased trimethylation of lysine 27 on the histone 3 (H3K27me3) level in granule neuron cells but not in cortical neurons or astrocytes. Furthermore, rRABV-EDAL infection induces more *Pcp411* mRNA transcription in granule neurons, while there are almost no obvious changes in cortical neurons or astrocytes. Consistently, compared with the parent virus RABV, reduced pathogenicity of rRABV-EDAL was observed in mice post-intranasal infection but not intramuscular infection. These results suggest that the lncRNA EDAL restricts RABV replication in a cell-specific and infection route-dependent manner.

Mitochondrial Dysfunction in Rabies Virus-Infected Human and Canine Brains.

Harsha, P., Ranganayaki, S., Yale, G., Dey, G., Mangalparthi, K., Yarlagadda, A., Chandrasekhar Sagar, B., Mahadevan, A., Srinivas Bharath, M., Mani, R.

28-02-2022

Neurochem Res

<https://doi.org/10.1007/s11064-022-03556-6>

Rabies is a fatal encephalitis caused by the Rabies lyssavirus (RABV). The presence of minimal neuropathological changes observed in rabies indicates that neuronal dysfunction, rather than neuronal death contributes to the fatal outcome. The role of mitochondrial changes has been suggested as a possible mechanism for neuronal dysfunction in rabies. However, these findings are mostly based on studies that have employed experimental models and laboratory-adapted virus. Studies on brain tissues from naturally infected human and animal hosts are lacking. The current study investigated the role of mitochondrial changes in rabies by morphological, biochemical and proteomic analysis of RABV-infected human and canine brains. Morphological analysis showed minimal inflammation with preserved neuronal and disrupted mitochondrial structure in both human and canine brains. Proteomic analysis revealed involvement of mitochondrial processes (oxidative phosphorylation, cristae formation, homeostasis and transport), synaptic proteins and autophagic pathways, with over-expression of subunits of mitochondrial respiratory complexes. Consistent with these findings, human and canine brains displayed elevated activities of complexes I ($p < 0.05$), IV ($p < 0.05$) and V ($p < 0.05$). However, this did not result in elevated ATP production ($p < 0.0001$), probably due to lowered mitochondrial membrane potential as noted in RABV-infected cells in culture. These could lead to mitochondrial dysfunction and mitophagy as indicated by expression of FKBP8 ($p < 0.05$) and PINK1 ($p < 0.001$)/PARKIN ($p > 0.05$) and ensuing autophagy, as shown by the status of LCIII ($p < 0.05$), LAMP1 ($p < 0.001$) and pertinent ultrastructural markers. We propose that altered mitochondrial bioenergetics and cristae architecture probably

induce mitophagy, leading to autophagy and consequent neuronal dysfunction in rabies.

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

Cheng, W., Su, Y., Hsu, H., Lin, Y., Chu, L., Huang, W., Lu, Y., Chiang, C., Hu, S.

28-02-2022

ACS Nano

<https://doi.org/10.1021/acsnano.1c09601>

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

A Stitch in Time: Operative and Nonoperative Laceration Repair Techniques.

Silverberg, B., Moyers, A., Wainblat, B., Cashio, P., Bernstein, K.

13-01-2022

Prim Care

<https://pubmed.ncbi.nlm.nih.gov/35125156>

Before repairing a laceration, consider the mechanism and severity of the injury. Gentle irrigation of the wound helps to remove microscopic infectious agents and larger debris. Not all foreign bodies are visible in plain radiographs. Certain wounds may be allowed to heal without operative intervention, but most patients prefer an approach using suture thread or tissue adhesive. Prophylaxis against tetanus, rabies, and/or bacterial infection should be considered. Clinical assessment of each wound is important to guide decisions about technique, anesthetic, suture material, and the interval period before nonabsorbable equipment can be removed.

Free-roaming dog population dynamics in Ranchi, India.

Evans, M., Gibson, A., Fielding, H., Ohal, P., Pandey, P., Kumar, A., Singh, S., Airikkala-Otter, I., Abela-Ridder, B.,

Gamble, L., Handel, I., Bronsvort, B., Mellanby, R., Mazeri, S.

01-01-2022

Res Vet Sci

<https://pubmed.ncbi.nlm.nih.gov/35007799>

Rabies causes approximately 20,000 human deaths in India each year. Nearly all of these occur following dog bites. Large-scale, high-coverage dog rabies vaccination campaigns are the cornerstone of rabies elimination strategies in both human and dog populations, although this is particularly challenging to achieve in India as a large proportion of the dog population are free-roaming and unowned. Further, little is known about free-roaming dog ecology in India which makes defining optimum vaccination strategies difficult. In this study, data collected using a mobile phone application during three annual mass vaccination and neutering (surgical sterilisation of both males and females) campaigns of free-roaming dogs in Ranchi, India (during which a total of 43,847 vaccinations, 26,213 neuter surgeries and 28,172 re-sight observations were made) were interrogated, using two novel approaches to estimate the proportion of neutered dogs that were lost from the city (assumed due to mortality or migration) between campaign years. Analysis revealed high losses of neutered dogs each year, ranging from 25.3% (28.2-22.8) to 55.8% (57.0-54.6). We also estimated that the total population declined by 12.58% (9.89-15.03) over the three-year period. This demonstrates that there is a high turnover of free-roaming dogs and that despite neutering a large number of dogs in an annual sterilisation campaign, the decline in population size was modest over a three-year time period. These findings have significant implications for the planning of rabies vaccination campaigns and population management programmes as well as highlighting the need for further research into the demographics of free-roaming, unowned dogs in India.

Exploring propriospinal neuron-mediated neural circuit plasticity using recombinant viruses after spinal cord injury.

Deng, L., Ravenscraft, B., Xu, X.

22-12-2021

Exp Neurol

<https://pubmed.ncbi.nlm.nih.gov/34953895>

Propriospinal neurons (PSNs) play a crucial role in motor control and sensory processing and contribute to plastic reorganization of spinal circuits responsible for recovery from spinal cord injury (SCI). Due to their scattered distribution and various intersegmental projection patterns, it is challenging to dissect the function of PSNs within the neuronal network. New genetically encoded tools, particularly cell-type-specific transgene expression methods using recombinant viral vectors combined with other genetic, pharmacologic, and optogenetic approaches, have enormous potential for visualizing PSNs in the neuronal circuits and monitoring and manipulating their activity. Furthermore, recombinant viral tools have been utilized to promote the intrinsic regenerative capacities of PSNs, towards manipulating the 'hostile' microenvironment for

improving functional regeneration of PSNs. Here we summarize the latest development in this fast-moving field and provide a perspective for using this technology to dissect PSN physiological role in contributing to recovery of function after SCI.

Dr. Abolghasem Bahrami (1894–1950): Physician, Pasteurian, and a Pioneer of Microbiology and Public Health Planning in Iran

Bahrami, F., Mostafavi, E.

01-03-2022

Iran Biomed J

<https://doi.org/10.52547/ibj.26.2.91>

Dr. Abolghasem Bahrami was among the generation of Iranian scientists in the early twentieth century who gained most of their knowledge through resources available inside the country. Educated at Dar-ul-Funun Medical School, he was a physician with a great talent in learning, especially self-teaching natural sciences and European languages. He joined the Pasteur Institute of Iran (IPI) at the early days of its foundation and became an integral contributor to this institution during the first twenty-five years of its mission. One of his first assignments at IPI was to help initiating an anti-rabies department by bringing back the rabies vaccine and its manufacturing equipment from Institut Pasteur of Paris. During his IPI years, aside from managerial tasks, he actively participated in upgrading the medical treatments and protocols used for controlling many infectious diseases. He functioned twice as the provisional director of IPI (1925-1926 and 1937-1946) and is considered as the first Iranian director of the Institute. Meanwhile, Dr. Bahrami was a significant contributor to the public health system and assumed several responsibilities such as Chief Quarantine Medical Officer, Chief of Public Health, and the Head of Public Health Administration, in order to improve public health planning throughout the country.

Rabies and the pandemic: lessons for One Health.

Nadal, D., Beeching, S., Cleaveland, S., Cronin, K., Hampson, K., Steenson, R., Abela-Ridder, B.

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Trans R Soc Trop Med Hyg

<https://doi.org/10.1093/trstmh/trab123>

This article examines the impact of coronavirus disease 2019 (COVID-19) on dog-mediated rabies, a neglected tropical disease that remains endemic in >65 countries. A globally agreed strategy for rabies elimination is underpinned by a One Health approach, coordinating human and animal health sectors and engaging communities. We present data on the scale and nature of COVID-19 disruption to rabies control programmes and the wider learning for One Health implementation. We argue that the global shift in health priorities caused by the pandemic, and consequent side-lining of animal health, will have broader ramifications for One Health

implementation and preparedness for future emergent zoonoses.

TRACHOME

Spontaneous corneal perforation in chronic trachoma.

Lopez-Yang, C., Morales-Mancillas, N., Domínguez-Varela, I., Rodríguez-García, A.

20-01-2022

J Fr Ophtalmol

<https://pubmed.ncbi.nlm.nih.gov/35067370>

Optimizing cluster survey designs for estimating trachomatous inflammation-follicular within trachoma control programs.

Gallini, J., Sata, E., Zerihun, M., Melak, B., Haile, M., Zeru, T., Gessese, D., Ayele, Z., Tadesse, Z., Callahan, E., Nash, S., Weiss, P.

26-12-2021

Int J Infect Dis

<https://pubmed.ncbi.nlm.nih.gov/34965463>

The World Health Organization recommends mass drug administration (MDA) with azithromycin to eliminate trachoma as a public health problem. MDA decisions are based on prevalence estimates from two-stage cluster surveys. There is a need to mathematically evaluate current trachoma survey designs. Our study aimed to characterize the effects of the number of units sampled on the precision and cost of trachomatous inflammation-follicular (TF) estimates. A population of 30 districts was simulated to represent the breadth of possible TF distributions in Amhara, Ethiopia. Samples of varying numbers of clusters (14-34) and households (10-60) were selected. Sampling schemes were evaluated based on precision, proportion of incorrect and low MDA decisions made, and estimated cost. The number of clusters sampled had a greater impact on precision than the number of households. The most efficient scheme depended on the underlying TF prevalence in a district. For lower prevalence areas (< 10%) the most cost-efficient design (providing adequate precision while minimizing cost) was 20 clusters of 20-30 households. For higher prevalence areas (> 10%), the most efficient design was 15-20 clusters of 20-30 households. For longer-running programs, using context-specific survey designs would allow for practical precision while reducing survey costs. Sampling 15 clusters of 20-30 households in suspected moderate-to-high prevalence districts and 20 clusters of 20-30 households in districts suspected to be near the 5% threshold appears to be a balanced approach.

ULCERE DE BURULI

Leg ulcers in childhood: A multicenter study in France.

Say, M., Tella, E., Boccara, O., Sauvage, M., Bourrat, E., Tian, Y., Monfort, J., Lok, C., Desierier, F., Beneton, N., Abasq-Thomas, C., Kupfer-Bessaguet, I., Mallet, S., Lacour, J., Plantin, P., Sigal, M., Mazereeuw-Hautier, J., Mahé, E., on behalf the Angio-Dermatology Group of the French Society of Dermatology, the Research Group of the French Society of Pediatric Dermatology

01-07-2021

Ann Dermatol Venerol

<https://pubmed.ncbi.nlm.nih.gov/34218940>

Leg ulcers in adults are a major public health concern. Their incidence increases with age and many causes have been identified, predominantly associated with vascular diseases. Leg ulcers in children and teenagers are less frequent. The aim of our study was to identify the causes of leg ulcers in children and teenagers, and to evaluate their management. This retrospective multicenter study was conducted by members of the Angio-dermatology Group of the French Society of Dermatology and of the French Society of Pediatric Dermatology. Data from children and teenagers (< 18 years), seen between 2008 and 2020 in 12 French hospitals for chronic leg ulcer (disease course > 4 weeks), were included. We included 27 patients, aged from 2.3 to 17.0 years. The most frequent causes of leg ulcer were: general diseases (n=9: pyoderma gangrenosum, dermatomyositis, interferonopathy, sickle cell disease, prolidase deficiency, scleroderma, Ehlers-Danlos syndrome), vasculopathies (n=8: hemangioma, capillary malformation, arteriovenous malformation), trauma (n=4: bedsores, pressure ulcers under plaster cast), infectious diseases (n=4: pyoderma, tuberculosis, Buruli ulcer) and neuropathies (n=2). Comorbidities (59.3%) and chronic treatments (18.5%) identified as risk factors for delayed healing were frequent. The average time to healing was 9.1 months. Leg ulcers are less frequent in children and teenagers than in adults and their causes differ from those in adults. Comorbidities associated with delayed healing must be identified and managed. Children and teenagers tend to heal faster than adults, but a multidisciplinary management approach is necessary.

PIAN

LEPRE

Leprosy as immune reconstitution inflammatory syndrome in patients living with HIV: Description of French Guiana's cases over 20 years and systematic review of the literature.

Mouchard, A., Blaizot, R., Graille, J., Couppié, P., Bertin, C.
04-03-2022

PLoS Negl Trop Dis

<https://doi.org/10.1371/journal.pntd.0010239>

HIV infection is highly prevalent in French Guiana, a territory where leprosy is also endemic. Since the introduction of Highly Active Antiretroviral Treatment (HAART) in the management of HIV, leprosy has been reported as part of the immune reconstitution inflammatory syndrome (IRIS). We aimed to present a general description of these forms of leprosy as IRIS, highlighting clinical and therapeutic specificities. A retrospective study was conducted in French Guiana, including patients living with HIV (PLHIV) with advanced infection (CD4 < 200/mm³) and developing leprosy or a leprosy reaction within six months of HAART initiation, from 2000 to 2020. Clinical, histological and biological data were collected for all these patients. Six patients were reported in French Guiana. A systematic review of the literature was conducted, and its results were added to an overall analysis. Overall, seventy-three PLHIV were included. They were mainly men (74%), aged 22-54 years (median 36 years), mainly from Brazil (46.5%) and India (32.8%). Most leprosy cases (56.2%) were borderline tuberculoid (BT). Leprosy reactions were frequent (74%), mainly type 1 reaction (T1R) (68.5%), sometimes intense with ulceration of skin lesions (22%). Neuritis was observed in 30.1% of patients. The outcome was always favorable under multidrug therapy (MDT), continuation of HAART and additional corticosteroid therapy in case of neuritis or ulceration. There was no relapse. Leprosy as IRIS in PLHIV mainly presents as a BT leprosy in a T1R state, sometimes with ulcerated skin lesions. Response to MDT is usually good. Systemic corticosteroids are necessary and efficient in case of neuritis.

High yield of retrospective active case finding for leprosy in Comoros.

Ortuño-Gutiérrez, N., Mzembaba, A., Baco, A., Braet, S., Younoussa, A., Salim, Z., Amidy, M., Grillone, S., Said, A., de Jong, B., Richardus, J., Hasker, E.

03-03-2022

PLoS Negl Trop Dis

<https://doi.org/10.1371/journal.pntd.0010158>

Serum Interleukin 6 Level and Nutrition Status as Potential Predictors of Clinical Leprosy Development Among Household Contacts in Endemic Areas.

Oktaria, S., Anfasa, F., Menaldi, S., Bramono, K., Nijsten, T., Thio, H.

02-02-2022

Open Forum Infect Dis

<https://doi.org/10.1093/ofid/ofac010>

Leprosy is a chronic infectious disease that can lead to severe lifelong disabilities. Close contacts of patients with leprosy have a higher risk of acquiring the disease. Nevertheless, there is a lack of reliable markers to predict *Mycobacterium leprae* infection. We aimed to identify new potential markers for developing clinical leprosy among contacts. Serum levels of interleukin (IL) 6, IL-8, IL-10, hemoglobin, ferritin, and transferrin saturation were measured in 67 patients with multibacillary leprosy (MB), 65 household contacts (HHCs) of MB patients, and 127 endemic controls (ECs). By means of multivariate logistic regression and receiver operating characteristic (ROC) analyses, we analyzed baseline variables and laboratory parameters that showed significant differences between MB in the HHC and EC groups and obtained the respective areas under the curve (AUC). Optimal cutoff values of the associated cytokines were also determined. Elevated IL-6 level was observed in MB patients compared to HHCs and ECs ($P = .022$ and $.0041$, respectively). Anemia and iron deficiency were also higher in the MB group compared to HHCs or ECs ($P < .001$). Likewise, we observed an increased risk of having MB leprosy in underweight HHCs (odds ratio [OR], 2.599 [95% confidence interval {CI}, .991-6.820]) and underweight ECs (OR, 2.176 [95% CI, 1.010-4.692]). Further ROC analysis showed that high serum IL-6 level, underweight, anemia, and iron deficiency can discriminate leprosy from their HHCs (AUC, 0.843 [95% CI, .771-.914]; $P = .000$; optimal cutoff value of IL-6 = 9.14 pg/mL). Our results suggest that serum IL-6 and nutrition status could serve as potential prognostic markers for the development of clinical leprosy in infected individuals.

Erythema Nodosum Leprosum Post-COVID-19 Vaccination: Endemic while Pandemic.

Fachler, T., Olshtain-Pops, K., Horev, L.

28-02-2022

J Eur Acad Dermatol Venereol

<https://doi.org/10.1111/jdv.18035>

Sensitivity of *Mycobacterium leprae* to Telacebec.

Lahiri, R., Adams, L., Thomas, S., Pethe, K.

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Emerg Infect Dis

<https://doi.org/10.3201/eid2803.210394>

The treatment of leprosy is long and complex, benefiting from the development of sterilizing, rapidly-acting drugs. Reductive evolution made *Mycobacterium leprae* exquisitely sensitive to Telacebec, a phase 2 drug candidate for tuberculosis. The unprecedented potency of Telacebec against *M. leprae* warrants further validation in clinical trials.

Mycobacterium leprae Infection in a Wild Nine-Banded Armadillo, Nuevo León, Mexico.

Vera-Cabrera, L., Ramos-Cavazos, C., Youssef, N., Pearce, C., Molina-Torres, C., Avalos-Ramirez, R., Gagneux, S., Ocampo-

Candiani, J., Gonzalez-Juarrero, M., Mayorga-Rodriguez, J., Mayorga-Garibaldi, L., Spencer, J., Jackson, M., Avanzi, C.

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Emerg Infect Dis

<https://doi.org/10.3201/eid2803.211295>

Nine-banded armadillos (*Dasypus novemcinctus*) are naturally infected with *Mycobacterium leprae* and are implicated in the zoonotic transmission of leprosy in the United States. In Mexico, the existence of such a reservoir remains to be characterized. We describe a wild armadillo infected by *M. leprae* in the state of Nuevo León, Mexico.

Algorithm Design for a Cytokine Release Assay of Antigen-Specific In Vitro Stimuli of Circulating Leukocytes to Classify Leprosy Patients and Household Contacts.

Marçal, P., de Souza, M., Gama, R., de Oliveira, L., Gomes, M., do Amaral, L., Pinheiro, R., Sarno, E., Moraes, M., Fairley, J., Martins-Filho, O., de Oliveira Fraga, L.

30-01-2022

Open Forum Infect Dis

<https://doi.org/10.1093/ofid/ofac036>

Immunological biomarkers have often been used as a complementary approach to support clinical diagnosis in several infectious diseases. The lack of commercially available laboratory tests for conclusive early diagnosis of leprosy has motivated the search for novel methods for accurate diagnosis. In the present study, we describe an integrated analysis of a cytokine release assay using a machine learning approach to create a decision tree algorithm. This algorithm was used to classify leprosy clinical forms and monitor household contacts. A model of *Mycobacterium leprae* antigen-specific in vitro assay with subsequent cytokine measurements by enzyme-linked immunosorbent assay was employed to measure the levels of tumor necrosis factor (TNF), interferon- γ , interleukin 4, and interleukin 10 (IL-10) in culture supernatants of peripheral blood mononuclear cells from patients with leprosy, healthy controls, and household contacts. Receiver operating characteristic curve analysis was carried out to define each cytokine's global accuracy and performance indices to identify clinical subgroups. Data demonstrated that TNF (control culture [CC]: AUC = 0.72; antigen-stimulated culture [MI]: AUC = 0.80) and IL-10 (CC: AUC = 0.77; MI: AUC = 0.71) were the most accurate biomarkers to classify subgroups of household contacts and patients with leprosy, respectively. Decision tree classifier algorithms for TNF analysis categorized subgroups of household contacts according to the operational classification with moderate accuracy (CC: 79% [48/61]; MI: 84% [51/61]). Additionally, IL-10 analysis categorized leprosy patients' subgroups with moderate accuracy (CC: 73% [22/30] and MI: 70% [21/30]). Together, our findings demonstrated that a cytokine release assay is a promising method to complement clinical diagnosis, ultimately contributing to effective control of the disease.

Bilateral ptosis/blepharitis due to lepromatous leprosy.

Iqbal, O., Langford, M., Flowers, A., Caldwell, J., Zaunbrecher, N., Byrd, W.

30-11-2021

Am J Ophthalmol Case Rep

<https://doi.org/10.1016/j.ajoc.2021.101236>

To underscore the importance of histopathological evaluation in cases presenting with a constellation of unusual ocular inflammation and physical findings. A 51-year-old male, presented with a chief complaint of worsening visual field loss due to droopy eyelids two months post excision of a right upper eyelid squamous cell carcinoma. His past medical history included chronic edematous facial features, chronic sinusitis, unexplained peripheral neuropathy, and worsening fatigue. Pre-blepharoplasty work-up revealed mechanical ptosis from lid edema, madarosis, a concave nasal bridge, pancytopenia, and numerous burn marks due to inadvertent injuries. Bilateral blepharoplasty was performed, and the excised tissue submitted for histopathological evaluation that revealed non-caseating granulomatous perineural inflammation with numerous acid-fast bacilli in dermal layers and nerves. These findings prompted a diagnosis of lepromatous leprosy with suspected bone marrow involvement. The source of the infection was unknown. The blepharoplasty restored his visual fields and multi-drug therapy (MDT) improved his general health and wellbeing with concomitant reductions of pancytopenia, fatigue, and facial edema. Biopsy histopathology, in patients with longstanding ocular adnexal inflammation, can facilitate diagnosis and treatment. To the authors' knowledge, this is an unusual ocular leprosy presentation and represents the first leprosy case diagnosed via blepharoplasty.

How do Positive Deviants Overcome Health-Related Stigma? An Exploration of Development of Positive Deviance Among People With Stigmatized Health Conditions in Indonesia.

Rai, S., Syurina, E., Peters, R., Putri, A., Irwanto, I., Zweekhorst, M.

14-12-2021

Qual Health Res

<https://doi.org/10.1177/10497323211058164>

A constructivist grounded theory approach was used to understand how some people living with stigmatized health conditions develop positive deviance to overcome stigma. We examined interviews from 13 identified positive deviants living with four different stigmatized health conditions (HIV, leprosy, schizophrenia, and diabetes) in Indonesia. Positive deviance develops in the form of psychological empowerment through improvement of self-belief and perception (intrapersonal component), development of understanding and skill to exert control in life (interactional component), and self-discovery of successful behaviors and strategies to avert stigma (behavioral component). Positive deviants, after being empowered, start empowering others affected by sharing their knowledge and

fostering social awareness and acceptance. The findings revealed the presence of problem-solving ability and agency within the community of stigmatized individuals in Indonesia and warrant researchers to partner with the community to expedite the diffusion of transferable positive deviant strategies within and outside the communities.

A probable case of leprosy from colonial period St. Vincent and the Grenadines, Southeastern Caribbean.

Nelson, G., Dodrill, T., Fitzpatrick, S.

13-11-2021

Int J Paleopathol

<https://pubmed.ncbi.nlm.nih.gov/34785426>

To document and differentially diagnose facial pathology found in an isolated skull from St. Vincent and the Grenadines, southeastern Caribbean. To directly date this individual using radiocarbon dating. Isolated skull recovered from Petite Mustique Island. Describe facial pathology occurring in this individual and compare with known diseases or disease processes that impact the craniofacial complex. Features of the rhinomaxillary syndrome are present, indicating a diagnosis of leprosy. Dating places the time of death to the late 18th or early 19th centuries. Analysis of the rhinomaxillary syndrome produces a diagnosis of early-stage leprosy in an individual that correlates with the apparent attempt to locate a leprosarium on Petite Mustique Island in the first decade of the 19th century. Location and time corroborate historical records of at least one attempt to locate a leprosarium on Petite Mustique Island. Only directly dated individual with leprosy in the western hemisphere and possibly the earliest yet recorded. This is an isolated find that is archaeologically unproven. Professional archaeological survey of Petite Mustique.

Paraphimosis as the only manifestation of type 2 lepra reaction.

Mehta, N., Agarwal, S., Khaitan, B., Gupta, V.

30-09-2021

Int J Dermatol

<https://doi.org/10.1111/ijd.15924>

TRYPANOSOMES (TRYPANOSOMIASE ET MALADIE DE CHAGAS)

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>

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. 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. 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. 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.

Trypanocidal effect of alcoholic extract of *Castanedia santamartensis* (Asteraceae) leaves is based on altered mitochondrial function.

Quintero-Pertuz, H., Veas-Albornoz, R., Carrillo, I., González-Herrera, F., Lapier, M., Carbonó-Delaho, E., Del Olmo, E., Feliciano, A., Kemmerling, U., Olea-Azar, C., Delporte, C., Maya, J.

28-02-2022

Biomed Pharmacother

<https://pubmed.ncbi.nlm.nih.gov/35240521>

The deficit of effective treatments for Chagas disease has led to searching for new substances with therapeutic potential. Natural products possess a wide variety of chemical structural motifs and are thus a valuable source of diverse lead compounds for the development of new drugs. *Castanedia santamartensis* is endemic to Colombia, and local indigenous communities often use it to treat skin sores from leishmaniasis; however, its mechanism of action against the infective form of *Trypanosoma cruzi* has not been determined. Thus, we performed chemical and biological studies of two alcoholic leaf extracts of *C. santamartensis* to identify their active fractions and relate them to a trypanocidal effect and evaluate their mechanism of action. Alcoholic extracts were obtained through cold maceration at room temperature and fractionated using classical column chromatography. Both ethanolic and methanolic extracts displayed activity against *T. cruzi*. Chemical

studies revealed that kaurenoic acid was the major component of one fraction of the methanolic extract and two fractions of the ethanolic extract of *C. santamartensis* leaves. Moreover, caryophyllene oxide, kaurenol, taraxasterol acetate, pentadecanone, and methyl and ethyl esters of palmitate, as well as a group of phenolic compounds, including ferulic acid, caffeic acid, chlorogenic acid, myricetin, quercitrin, and cryptochlorogenic acid were identified in the most active fractions. Kaurenoic acid and the most active fractions CS400 and CS402 collapsed the mitochondrial membrane potential in trypomastigotes, demonstrating for the first time the likely mechanism against *T. cruzi*, probably due to interactions with other components of the fractions.

Antioxidant defence system as a rational target for Chagas disease and Leishmaniasis chemotherapy.

Santi, A., Murta, S.

28-02-2022

Mem Inst Oswaldo Cruz

<https://pubmed.ncbi.nlm.nih.gov/35239945>

Chagas disease and leishmaniasis are neglected tropical diseases caused by the protozoan parasites *Trypanosoma cruzi* and *Leishmania* spp., respectively. They are among the most important parasitic diseases, affecting millions of people worldwide, being a considerable global challenge. However, there is no human vaccine available against *T. cruzi* and *Leishmania* infections, and their control is based mainly on chemotherapy. Treatments for Chagas disease and leishmaniasis have multiple limitations, mainly due to the high toxicity of the available drugs, long-term treatment protocols, and the occurrence of drug-resistant parasite strains. In the case of Chagas disease, there is still the problem of low cure rates in the chronic stage of the disease. Therefore, new therapeutic agents and novel targets for drug development are urgently needed. Antioxidant defence in Trypanosomatidae is a potential target for chemotherapy because the organisms present a unique mechanism for trypanothione-dependent detoxification of peroxides, which differs from that found in vertebrates. Cellular thiol redox homeostasis is maintained by the biosynthesis and reduction of trypanothione, involving different enzymes that act in concert. This study provides an overview of the antioxidant defence focusing on iron superoxide dismutase A, tryparedoxin peroxidase, and ascorbate peroxidase and how the enzymes play an important role in the defence against oxidative stress and their involvement in drug resistance mechanisms in *T. cruzi* and *Leishmania* spp.

Worldwide Control and Management of Chagas Disease in a New Era of Globalization: a Close Look at Congenital *Trypanosoma cruzi* Infection.

Abras, A., Ballart, C., Fernández-Arévalo, A., Pinazo, M., Gascón, J., Muñoz, C., Gállego, M.

03-03-2022

Clin Microbiol Rev

<https://doi.org/10.1128/cmr.00152-21>

Population movements have turned Chagas disease (CD) into a global public health problem. Despite the successful implementation of subregional initiatives to control vectorial and transfusional *Trypanosoma cruzi* transmission in Latin American settings where the disease is endemic, congenital CD (cCD) remains a significant challenge. In countries where the disease is not endemic, vertical transmission plays a key role in CD expansion and is the main focus of its control. Although several health organizations provide general protocols for cCD control, its management in each geopolitical region depends on local authorities, which has resulted in a multitude of approaches. The aims of this review are to (i) describe the current global situation in CD management, with emphasis on congenital infection, and (ii) summarize the spectrum of available strategies, both official and unofficial, for cCD prevention and control in countries of endemicity and nonendemicity. From an economic point of view, the early detection and treatment of cCD are cost-effective. However, in countries where the disease is not endemic, national health policies for cCD control are nonexistent, and official regional protocols are scarce and restricted to Europe. Countries of endemicity have more protocols in place, but the implementation of diagnostic methods is hampered by economic constraints. Moreover, most protocols in both countries where the disease is endemic and those where it is not endemic have yet to incorporate recently developed technologies. The wide methodological diversity in cCD diagnostic algorithms reflects the lack of a consensus. This review may represent a first step toward the development of a common strategy, which will require the collaboration of health organizations, governments, and experts in the field.

Cardiac graft loss in transplant recipient with Chagas disease.

Avila, M., Belfort, D., Leite, V., Demarche, L., Ayub-Ferreira, S.

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Am J Transplant

<https://doi.org/10.1111/ajt.16919>

Effective residual convolutional neural network for Chagas disease parasite segmentation.

Ojeda-Pat, A., Martin-Gonzalez, A., Brito-Loeza, C., Ruiz-Piña, H., Ruz-Suarez, D.

01-03-2022

Med Biol Eng Comput

<https://doi.org/10.1007/s11517-022-02537-9>

Considered a neglected tropical pathology, Chagas disease is responsible for thousands of deaths per year and it is caused by the parasite *Trypanosoma cruzi*. Since many infected people can remain asymptomatic, a fast diagnosis is necessary for proper intervention. Parasite microscopic observation in blood samples is the gold standard method to diagnose Chagas disease in its initial phase; however, this is a time-consuming procedure, requires expert intervention, and there is currently

no efficient method to automatically perform this task. Therefore, we propose an efficient residual convolutional neural network, named Res2Unet, to perform a semantic segmentation of *Trypanosoma cruzi* parasites, with an active contour loss and improved residual connections, whose design is based on Heun's method for solving ordinary differential equations. The model was trained on a dataset of 626 blood sample images and tested on a dataset of 207 images. Validation experiments report that our model achieved a Dice coefficient score of 0.84, a precision value of 0.85, and a recall value of 0.82, outperforming current state-of-the-art methods. Since Chagas disease is a severe and silent illness, our computational model may benefit health care providers to give a prompt diagnose for this worldwide affection.

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

McLaughlin, E., Rubio-Pena, K., Dujancourt-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.

Transcriptomics Applied to the Study of Chagas Disease Vectors.

Borsatto, K., Coronado, M., Galvão, C., Arni, R., Alevi, K.
28-02-2022

Am J Trop Med Hyg

<https://doi.org/10.4269/ajtmh.21-0636>

Chagas disease is a neglected disease caused by the protozoan *Trypanosoma cruzi*, and is transmitted mainly by the feces of contaminated triatomines. Knowledge of the biological, ecological, behavioral, genetic, taxonomic, and systematic aspects of these vectors can contribute to the planning of vector control programs, because all species are considered to be potential vectors of Chagas disease. Transcriptomic studies, in general, provided a new view of the physiology of triatomines (aiding in the knowledge of reproductive aspects of the hematophagy process and even the immune system and the sensory apparatus) and even contributed, as a new tool, to the taxonomy and systematics of these insects. Thus, we conducted a review of the transcriptomic studies on Chagas disease vectors.

Reviewing a Decade of Outpatient Tropical Medicine in Houston, Texas.

Kaplan, J., Centeno, F., Hayon, J., Bottazzi, M., Hotez, P., Weatherhead, J., Clark, E., Woc-Colburn, L.
28-02-2022

Am J Trop Med Hyg

<https://doi.org/10.4269/ajtmh.21-1059>

Tropical diseases cause significant morbidity among the world's poorest populations. Although more common in low- and middle-income countries, tropical diseases are also found among underserved populations living in high-income countries such as the United States. The National School of Tropical Medicine at Baylor College of Medicine and the Harris Health System founded a tropical medicine clinic-the Harris Health Tropical Medicine Clinic (HHTMC)-in Houston in 2011 in response to tropical disease-related morbidity in Texas. We conducted a retrospective chart review of a sample of patients older than 18 years of age who were referred to the HHTMC between October 2011 and January 2020. Of the 523 patients reviewed, 185 (35.4%) had mycobacterial infections, 184 (35.2%) had parasitic infections, 38 (7.3%) had fungal infections, 16 (3.1%) had eosinophilia without a confirmed clinical diagnosis, 28 (5.4%) had bacterial infections, and 13 (2.5%) had viral infections. The most common infections overall were extrapulmonary and latent tuberculosis (n = 169), neurocysticercosis (n = 78), strongyloidiasis (n = 28), Chagas disease (n = 25), and schistosomiasis (n = 12). The epidemiology of tropical diseases in the United States is understudied at national and regional levels. This 10-year retrospective study

contributes to bridging this knowledge gap by detailing the frequencies of tropical disease diagnoses made at the HHTMC in Houston, TX. These data highlight areas for advancement in the field of tropical medicine within the United States, such as improving front-line health-care provider education; establishing tropical medicine clinics in areas of high prevalence such as the Gulf Coast, Appalachia, and urban areas; and developing comprehensive, systematic national tropical disease screening programs and patient registries.

N⁶-modification of 7-Deazapurine nucleoside analogues as Anti-*Trypanosoma cruzi* and anti-*Leishmania* agents: Structure-activity relationship exploration and In vivo evaluation.

Lin, C., Jaén Batista, D., Mazzeti, A., Donola Girão, R., de Oliveira, G., Karalic, I., Hulpia, F., Soeiro, M., Maes, L., Caljon, G., Van Calenbergh, S.

31-01-2022

Eur J Med Chem

<https://pubmed.ncbi.nlm.nih.gov/35144125>

Chagas disease and leishmaniasis are two poverty-related neglected tropical diseases that cause high mortality and morbidity. Current treatments suffer from severe limitations and novel, safer and more effective drugs are urgently needed. Both *Trypanosoma cruzi* and *Leishmania* are auxotrophic for purines and absolutely depend on uptake and assimilation of host purines. This led us to successfully explore purine nucleoside analogues as chemotherapeutic agents against these and other kinetoplastid infections. This study extensively explored the modification of the 6-amino group of tubercidin, a natural product with trypanocidal activity but unacceptable toxicity for clinical use. We found that mono-substitution of the amine with short alkyls elicits potent and selective antitrypanosomal and antileishmanial activity. The methyl analogue 15 displayed the best in vitro activity against both *T. cruzi* and *L. infantum* and high selectivity versus host cells. Oral administration for five consecutive days in an acute Chagas disease mouse model resulted in significantly reduced peak parasitemia levels (75, 89 and 96% with 12.5, 25 and 50 mg/kg/day, respectively). as well as increased animal survival rates with the lower doses (83 and 67% for 12.5 and 25 mg/kg/day, respectively).

POLIE suppresses telomerase-mediated telomere G-strand extension and helps ensure proper telomere C-strand synthesis in trypanosomes.

Rabbani, M., Tonini, M., Afrin, M., Li, B.

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Nucleic Acids Res

<https://doi.org/10.1093/nar/gkac023>

Trypanosoma brucei causes human African trypanosomiasis and sequentially expresses distinct VSGs, its major surface antigen, to achieve host immune evasion. VSGs are monoallelically expressed from subtelomeric loci, and telomere proteins regulate VSG monoallelic expression and VSG

switching. *T. brucei* telomerase is essential for telomere maintenance, but no regulators of telomerase have been identified. *T. brucei* appears to lack OB fold-containing telomere-specific ssDNA binding factors that are critical for coordinating telomere G- and C-strand syntheses in higher eukaryotes. We identify POLIE as a telomere protein essential for telomere integrity. POLIE-depleted cells have more frequent VSG gene conversion-mediated VSG switching and an increased amount of telomeric circles (T-circles), indicating that POLIE suppresses DNA recombination at the telomere/subtelomere. POLIE-depletion elongates telomere 3' overhangs dramatically, indicating that POLIE is essential for coordinating DNA syntheses of the two telomere strands. POLIE depletion increases the level of telomerase-dependent telomere G-strand extension, identifying POLIE as the first *T. brucei* telomere protein that suppresses telomerase. Furthermore, depletion of POLIE results in an elevated telomeric C-circle level, suggesting that the telomere C-strand experiences replication stress and that POLIE may promote telomere C-strand synthesis. Therefore, *T. brucei* uses a novel mechanism to coordinate the telomere G- and C-strand DNA syntheses.

Chronic rapamycin pretreatment modulates arginase/inducible nitric oxide synthase balance attenuating aging-dependent susceptibility to *Trypanosoma cruzi* infection and acute myocarditis.

Pereira-Santos, M., Gonçalves-Santos, E., Souza, M., Caldas, I., Lima, G., Gonçalves, R., Novaes, R.

27-12-2021

Exp Gerontol

<https://pubmed.ncbi.nlm.nih.gov/34968674>

Considering the efficacy of rapamycin in increasing lifespan and healthspan, attenuating the aging-dependent immunological decline, we compared the evolution of *Trypanosoma cruzi* infection and acute myocarditis in young and elderly mice untreated and chronically treated with this drug. Five groups were investigated: young uninfected and infected, elderly uninfected and infected with *Trypanosoma cruzi* untreated and treated with rapamycin (4 mg/kg every 3 days) from the 8th to the 96th week of age. Seven days after the last treatment, elderly mice were inoculated with *T. cruzi*. Young animals were infected at 8-weeks-old. Untreated elderly mice exhibited increase parasitemia, parasite load and myocarditis, which were associated to down-regulation in IL-2, IL-6, IFN- γ , TNF, anti-*T. cruzi* immunoglobulin G (IgG) total, IgG1 and IgG2a plasma levels, inducible nitric oxide synthase (iNOS) gene expression and nitric oxide (NO) cardiac production, as well as upregulation in Arginase-1 gene expression and arginase activity compared to young animals. These parameters were improved in rapamycin-pretreated elderly mice, which exhibited a better parasitological control, reduced heart inflammation and microstructural damage. These responses were associated with a better balance between Th1 and Th2 effectors similar to that observed in young animals, including an improved activation of Th1 cytokines and the iNOS pathway

that positively regulates NO biosynthesis, contradicting the predominant activation of the arginase pathway in untreated elderly animals. Thus, our findings suggest that chronic pretreatment with rapamycin can attenuate immunosenescence in mice, contributing to prolong parasite resistance and attenuate acute myocarditis in elderly host challenged by *T. cruzi*.

Chagas disease, COVID-19 and P2X7 receptor.

de Souza Ferreira Pereira, C., Xavier Faria, R.

06-01-2022

Scand J Immunol

<https://doi.org/10.1111/sji.13135>

Homology modelling of *Trypanosoma brucei* major surface proteases and molecular docking of variant surface glycoproteins and inhibitor ligands for drug design.

Marufu, L., Coetzer, T.

11-12-2021

J Mol Graph Model

<https://pubmed.ncbi.nlm.nih.gov/34920394>

Trypanosomes, which cause animal African trypanosomiasis, escape host immune responses by renewing their variable surface glycoprotein (VSG) coat. Chemotherapy is currently the only form of external intervention available. However, the efficacy of current trypanocides is poor due to overuse leading to an increase in drug resistance. Major surface proteases (MSPs) of trypanosomes, which are zinc-dependent metalloproteases, are possible drug targets. A *Trypanosoma brucei* MSP-B (TbMSP-B) mediates parasite antigenic variation via cleavage of 60% of VSG molecules. Whilst TbMSP-A has no apparent role in VSG cleavage; it is not known if TbMSP-C is involved in VSG cleavage. In this study, three-dimensional structures of TbMSP-A, TbMSP-B and TbMSP-C were modelled. By comparing the docking poses of the C-terminal domains of VSG substrates into the models, TbMSP-C showed an affinity for similar VSG substrate sites as TbMSP-B, but these sites differed from those recognised by TbMSP-A. This observation suggests that TbMSP-C may be involved in VSG cleavage during antigenic variation. Furthermore, by docking small inhibitor ligands into the TbMSP-B and TbMSP-C homology models, followed by molecular dynamics simulations, ligands with potential anti-trypanosomal activity were identified. Docking studies also revealed the depth of the S₁' pockets of TbMSP-B and TbMSP-C, which is influential in ligand and substrate binding, thereby identifying the protease subsite pocket that should be targeted in drug design.

Exploring the role of glycoprotein hormone GPA2/GPB5 in the medically important insect, *Rhodnius prolixus*.

Al-Dailami, A., Leyria, J., Orchard, I., Lange, A.

13-12-2021

Peptides

<https://pubmed.ncbi.nlm.nih.gov/34915093>

Glycoprotein hormones are formed by the heterodimerization of alpha and beta subunits. In vertebrates, there are five glycoprotein hormones, four of which have a common alpha subunit (GPA1) bound to a specific beta subunit (GPB1, GPB2, GPB3, or GPB4), and the fifth, thyrostimulin, is formed by the dimerization of GPA2 and GPB5 subunits. These hormones mediate physiological events such as development, metabolism, and reproduction, although the functional role of thyrostimulin in vertebrates has not been fully elucidated. Recent reports in invertebrates, specifically in holometabolous insects, suggest that GPA2/GPB5 plays a critical role in development, diuresis, and reproduction. In this study, we clone and characterize the transcripts for the glycoprotein hormone GPA2/GPB5 and its receptor (LGR1) in fifth instar *Rhodnius prolixus*, a hemimetabolous insect vector of Chagas disease. Sequence analyses reveals considerable identity and similarity between GPA2/GPB5 and LGR1 and those reported in other arthropod species. Quantitative PCR (qPCR) shows that both subunit transcripts, GPA2 and GPB5, and LGR1 transcripts are present in a variety of tissues, with greatest expression of the subunits in the central nervous system (CNS) and highest LGR1 expression in the Malpighian tubules (MT). Results from temporal qPCR analyses reveal a decrease in transcript expression 24 h after feeding, followed by an increase as the days post-feeding advance. Using immunohistochemistry, we show that GPB5 is expressed throughout the CNS, and importantly is present in neurosecretory cells in the brain and abdominal neuromeres and their neurohemal organs, indicating a neurohormonal role for this signaling pathway. A reduction in LGR1 transcript expression (via RNA interference) led to a greater weight loss and mortality rate in unfed insects. In addition, when a blood meal is offered, the insects with reduced LGR1 consume a significantly smaller blood meal and have higher mortality rates as the days post-feeding advance. Overall, the results suggest that the GPA2/GPB5 signaling pathway may play roles during a prolonged unfed state and in feeding-related events.

Occurrence and spatial distribution of triatomines (Hemiptera: Reduviidae) in the urban area of the municipality of Montes Claros, Northern Minas Gerais, Brazil.

Campos, M., Gonçalves, T., Ursine, R., Marinho, S., Rodríguez Moreno, A., Diotaiuti, L., Damasceno, R., Ferreira, A., Ribeiro, A., Sabino, E., Vieira, T.
25-11-2021

Zoonoses Public Health

<https://doi.org/10.1111/zph.12897>

The north of the Brazilian state of Minas Gerais is classified as an area of high risk of vectorial transmission of Chagas disease (CD) or of reestablishing transmission in the home, but the Chagas disease control programme is disjointed. The study evaluated the occurrence, natural infection and the spatial distribution of species of triatomines associated with climatic

variations in the urban area of Montes Claros, a municipality endemic to CD in the north of Minas Gerais, Brazil. Triatomine data were obtained from passive entomological surveillance actions of the Chagas Disease Control Program (Programa de Controle de Doença de Chagas-PCDCh), registered by the Zoonosis Control Center (Centro de Controle de Zoonoses-CCZ) from 2009 to 2019. A total of 277 triatomines belonging to eight species were collected, and of these, 203 insects were examined. It was found that 46.2% of triatomines were captured inside the home and 8.3% around the home. The natural infection rate was 6.9%; 14 specimens showed natural infection by *Trypanosoma cruzi* (12 females and 2 males), and of these, 13 were found in the home and one in an uninformed location. The number of triatomine records collected was significantly higher in the month of September ($p = .01$), and there was an inverse correlation between the number of triatomines and the relative humidity of the air ($p < .001$). It was verified that the highest triatomine densities are located in transition areas between urban infrastructure (32.12%) and pasture (25.72%). The diversity of species of triatomines infected with *T. cruzi* in residential units in urban areas in the municipality of Montes Claros is worrying, as it suggests a potential risk of transmission of the parasite to domestic animals and humans.

Unexpected case of chagas disease reactivation in endomyocardial biopsy for evaluation of cardiac allograft rejection.

Hamilton, M., Sciaudone, M., Chang, P., Bowman, N., Andermann, T., Bartelt, L., Jaganathan, S., Rose-Jones, L., Andrews, M., Singer, B.
03-11-2021

Cardiovasc Pathol

<https://pubmed.ncbi.nlm.nih.gov/34742866>

Acute Chagas disease reactivation (CDR) after cardiac transplantation is a well-known phenomenon in endemic countries of Central and South America and Mexico, but is rare outside of those countries. In this report, we describe a case of a 49-year-old male who presented 25 weeks after heart transplant with clinical features concerning for acute rejection, including malaise, anorexia, weight loss, and fever. His immunosuppression therapy included tacrolimus, mycophenolate, and prednisone. An endomyocardial biopsy revealed lymphocytic and eosinophilic inflammation, myocyte damage, and rare foci of intracellular organisms consistent with *Trypanosoma cruzi* amastigotes. The patient had no known history of Chagas disease. Upon additional questioning, the patient endorsed bites from reduviid bugs during childhood in El Salvador. Follow-up serum PCR testing was positive for *T. cruzi* DNA. Tests for other infectious organisms and donor specific antibodies were negative. This case illustrates the striking clinical and histologic similarities between acute cellular rejection and acute CDR with cardiac involvement in heart transplant patients, and thus emphasizes the importance

of pre-transplant testing for Chagas in patients with epidemiologic risk factors.

High chromosomal mobility of rDNA clusters in holocentric chromosomes of Triatominae, vectors of Chagas disease (Hemiptera-Reduviidae).

Pita, S., Lorite, P., Cuadrado, A., Panzera, Y., De Oliveira, J., Alevi, K., Rosa, J., Freitas, S., Gómez-Palacio, A., Solari, A., Monroy, C., Dorn, P., Cabrera-Bravo, M., Panzera, F.
03-11-2021

Med Vet Entomol

<https://doi.org/10.1111/mve.12552>

The subfamily Triatominae (Hemiptera-Reduviidae) includes more than 150 blood-sucking species, potential vectors of the protozoan *Trypanosoma cruzi*, causative agent of Chagas disease. A distinctive cytogenetic characteristic of this group is the presence of extremely stable chromosome numbers. Unexpectedly, the analyses of the chromosomal location of ribosomal gene clusters and other repetitive sequences place Triatominae as a significantly diverse hemipteran subfamily. Here, we advance the understanding of Triatominae chromosomal evolution through the analysis of the 45S rDNA cluster chromosomal location in 92 Triatominae species. We found the 45S rDNA clusters in one to four loci per haploid genome with different chromosomal patterns: On one or two autosomes, on one, two or three sex chromosomes, on the X chromosome plus one to three autosomes. The movement of 45S rDNA clusters is discussed in an evolutionary context. Our results illustrate that rDNA mobility has been relatively common in the past and in recent evolutionary history of the group. The high frequency of rDNA patterns involving autosomes and sex chromosomes among closely related species could affect genetic recombination and the viability of hybrid populations, which suggests that the mobility of rDNA clusters could be a driver of species diversification.

Refolding of metacaspase 5 from *Trypanosoma cruzi*, structural characterization and the influence of c-terminal in protein recombinant production.

De Lima, J., Santos, M., Andreassa, E., Kurt, L., Carvalho, P., De Souza, T.

30-10-2021

Protein Expr Purif

<https://pubmed.ncbi.nlm.nih.gov/34728367>

Metacaspases are known to have a fundamental role in apoptosis-like, a programmed cellular death (PCD) in plants, fungi, and protozoans. The last includes several parasites that cause diseases of great interest to public health, mostly without adequate treatment and included in the neglected tropical diseases category. One of them is *Trypanosoma cruzi* which causes Chagas disease and has two metacaspases involved in its PCD: TcMCA3 and TcMCA5. Their roles seemed different in PCD, TcMCA5 appears as a proapoptotic protein negatively regulated by its C-terminal sequence, while TcMCA3 is described as a cell cycle regulator. Despite this, the precise role

of TcMCA3 and TcMCA5 and their atomic structures remain elusive. Therefore, developing methodologies to allow investigations of those metacaspases is relevant. Herein, we produced full-length and truncated versions of TcMCA5 and applied different strategies for their folded recombinant production from *E. coli* inclusion bodies. Biophysical assays probed the efficacy of the production method in providing a high yield of folded recombinant TcMCA5. Moreover, we modeled the TcMCA5 protein structure using experimental restraints obtained by XLMS. The experimental design for novel methods and the final protocol provided here can guide studies with other metacaspases. The production of TcMCA5 allows further investigations as protein crystallography, HTS drug discovery to create potential therapeutic in the treatment of Chagas' disease and in the way to clarify how the PCD works in the parasite.

Detection of *Trypanosoma cruzi* infection by PCR in *Canis lupus familiaris* and their ectoparasites in Chile.

Opazo, A., Bacigalupo, A., Urrutia, S., Chávez, G.
30-10-2021

Med Vet Entomol

<https://doi.org/10.1111/mve.12554>

Chronic Chagas disease affects humans and animals, involving rural and urban inhabitants. Dogs participate in the maintenance and transmission of *Trypanosoma cruzi*. The objective of this study was to evaluate the presence of *T. cruzi* in dogs and their ticks and fleas, in a rural area of Central Chile. *Trypanosoma cruzi* was detected by PCR both in dogs and ectoparasites. From the blood samples obtained, 57% were infected by *T. cruzi*, 5.4% of the ticks detected were positive, and all fleas were negative. Additionally, we performed electrocardiograms and found supraventricular arrhythmia in 44% of *T. cruzi*-positive dogs. Nevertheless, their risk for supraventricular arrhythmias was not higher in infected versus noninfected dogs. Considering the detected infection levels, dogs act as *T. cruzi* hosts in Central Chile, and ticks could be used as an indicator of infection when blood samples are not available. However, at this point, there is no indication that these ticks could pass on the parasite to another host. Periodic ectoparasitic treatment of pets should reduce the chance of vectorial transmission of *T. cruzi* and improve canine health; however, this is an uncommon practice among rural communities, so governmental programs are encouraged to tackle this problem.

Infections by trypanosomatid (Kinetoplastida: Trypanosomatidae) in triatomines (Hemiptera: Triatominae): A spatiotemporal assessment in an endemic area for Chagas disease.

Silva, T., Ferrer-Miranda, E., de Oliveira, J., Santoro, K., Alves, L., de Barros, L., Ramos, R., de Carvalho, G.
28-10-2021

Zoonoses Public Health

<https://doi.org/10.1111/zph.12898>

This research analysed the spatiotemporal distribution of triatomines infected by trypanosomatid parasites in an endemic region for Chagas disease, in the state of Pernambuco, Northeastern Brazil. The database included the total number of triatomines captured from intradomicile and peridomicile areas, as well as the infection rate (IR) by trypanosomatid. The G_i^* by Getis-Ord method was used to statistically identify significant concentration clusters and the IR of triatomines by trypanosomatids. A generalized linear regression model with a binomial distribution was used to evaluate the probability of finding an IR by trypanosomatids. Overall, of 4,800 triatomines examined, trypanosomatid forms similar to *Trypanosoma cruzi* were detected in 10.29% of them, and the majority of positive specimens (98.17%) were collected at intradomicile. The geospatial analyses identified triatomines clusters in intradomicile and peridomicile environments. According to the logistic regression data for species (*Panstrongylus lutzi*, *P. megistus*, *Triatoma brasiliensis* and *T. pseudomaculata*), the probability of detection of *T. cruzi* infection remains constant in up to 50 specimens examined or more. The findings of this research revealed a scenario never studied in this area through this type of spatiotemporal analysis, which is essential to identify areas of vulnerability for the occurrence of these vectors and consequently for Chagas disease.

LEISHMANIOSE

Low expression of hypoxia-inducible factor-1 α 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 Lonardon, 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)-1 α 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-1 α , 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-1 α 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-1 α gene transcription seemed to be down-modulated by *L. (Viannia)* infection and was less inhibited by *L. lainsoni* and *L. naiffi* when compared to *L. braziliensis*. Animals with *L. lainsoni* and *L. naiffi* showed better control of the disease. Further studies are necessary to evaluate the mechanism influencing HIF-1 α expression and its role on CL protection; such research could elucidate potential use of HIF-1 α as a therapeutic target.

In vitro leishmanicidal activity of two cholesterol derivatives.

Isaac-Márquez, A., Lezama-Dávila, C.

05-03-2022

World J Microbiol Biotechnol

<https://doi.org/10.1007/s11274-022-03248-x>

We evaluated the leishmanicidal activity of commercially available 5 α -cholest-7-en-3 β -ol [5 α -chol], (+)-4-cholesten-3-one [(+)-4-chol] and the equimolar mixture of the two of them in promastigotes and amastigotes of two different strains of *Leishmania mexicana* (LCL) and (DCL). The leishmanicidal effectiveness of these sterols was determined by promastigote growth-kinetic experiments and promastigote viability using the propidium iodide staining procedure. The proliferation test was performed using the CFSE (5-Carboxyfluorescein N-succinimidyl ester) staining of parasites at different time points. To determine the leishmanicidal effectiveness of these sterols in amastigotes, we evaluated parasite killing inside of macrophages at different time points. The trypan blue exclusion test was used to determine cytotoxicity of sterols in uninfected macrophages. We included in all experiments a control group of parasites treated with 2% DMSO (Dimethyl Sulfoxide) and another one treated with the reference drug sodium stibogluconate (Sb). Our results showed that the equimolar mixture at 2000 times lower concentration presented similar leishmanicidal activity as Sb. This mixture was similarly effective at 100 times lower concentration than individual sterols tested separately indicating the existence of a synergistic effect against LCL and DCL parasites. The therapeutic index of the equimolar mixture was 10,000-16,000 times higher than the one recorded by Sb and was not cytotoxic to macrophages. Therefore, the equimolar mixture of 5 α -Chol and (+)-4-chol may represent a potential alternative for the treatment of cutaneous leishmaniasis.

Autochthonous transmission of *Leishmania donovani* and *Leishmania major* with all the components of infection cycle at Europe's doorstep.

Özbilgin, A., Tunalı, V., Akar, Ş., Yıldırım, A., Şen, S., Çavuş, I., Zorbozan, O., Gündüz, C., Turgay, N., İnanır, I.
01-03-2022

Acta Trop

<https://pubmed.ncbi.nlm.nih.gov/35245491>

Leishmaniasis is a vector-borne disease and dogs may act as urban reservoirs. Turkey and most of the Mediterranean basin countries are endemic for leishmaniasis. In this study, it is aimed to report the autochthonous leishmaniasis cases, with all the components of the infection cycle (reservoir, vector, and the host) in a region close to Europe. Nine human and four canine autochthonous leishmaniasis cases were included in the study. Direct microscopy, culture methods, serological, and molecular tests were applied to the samples obtained from the cases. VL and CL patients consisted of 2 *L. infantum*, 1 *L. donovani*, 2 *L. tropica*, and 2 *L. tropica*, 1 *L. major*, 1 *L. infantum* infected patients respectively. CanL cases were infected with *L. infantum*, *L. donovani*, *L. tropica*, and *L. major*. All the cases were autochthonous cases located in Manisa province. As Greece and all the Mediterranean basin countries in Europe share competent vectors, it is concluded that the detection of all 4 species of *Leishmania* parasites in such proximity to Europe poses an important public health threat for Europe. This study reports all four species of *Leishmania* spp., including *L. major* and *L. donovani* in close proximity to continental Europe.

Broad-spectrum in vitro activity of macrophage infectivity potentiator inhibitors against Gram-negative bacteria and *Leishmania major*.

Iwasaki, J., Lorimer, D., Vivoli-Vega, M., Kibble, E., Peacock, C., Abendroth, J., Mayclin, S., Dranow, D., Pierce, P., Fox, D., Lewis, M., Bzdyl, N., Kristensen, S., Inglis, T., Kahler, C., Bond, C., Hasenkopf, A., Seufert, F., Schmitz, J., Marshall, L., Scott, A., Norville, I., Myler, P., Holzgrabe, U., Harmer, N., Sarkar-Tyson, M.

04-03-2022

J Antimicrob Chemother

<https://pubmed.ncbi.nlm.nih.gov/35245364>

The macrophage infectivity potentiator (Mip) protein, which belongs to the immunophilin superfamily, is a peptidyl-prolyl cis/trans isomerase (PPIase) enzyme. Mip has been shown to be important for virulence in a wide range of pathogenic microorganisms. It has previously been demonstrated that small-molecule compounds designed to target Mip from the Gram-negative bacterium *Burkholderia pseudomallei* bind at the site of enzymatic activity of the protein, inhibiting the in vitro activity of Mip. In this study, co-crystallography experiments with recombinant *B. pseudomallei* Mip (BpMip) protein and Mip inhibitors, biochemical analysis and computational modelling were used to predict the efficacy of lead compounds for broad-spectrum activity against other pathogens. Binding activity of three lead compounds targeting BpMip was verified using surface plasmon resonance

spectroscopy. The determination of crystal structures of BpMip in complex with these compounds, together with molecular modelling and in vitro assays, was used to determine whether the compounds have broad-spectrum antimicrobial activity against pathogens. Of the three lead small-molecule compounds, two were effective in inhibiting the PPIase activity of Mip proteins from *Neisseria meningitidis*, *Klebsiella pneumoniae* and *Leishmania major*. The compounds also reduced the intracellular burden of these pathogens using in vitro cell infection assays. These results indicate that Mip is a novel antivirulence target that can be inhibited using small-molecule compounds that prove to be promising broad-spectrum drug candidates in vitro. Further optimization of compounds is required for in vivo evaluation and future clinical applications.

A trespasser from a foreign land? A case report of primary mucosal leishmaniasis.

Fleissig, Y., Dan-Gur, M., Michael-Gayego, A., Maly, A., Tabib, R., Jaffe, C., Korem, M.

03-03-2022

BMC Infect Dis

<https://doi.org/10.1186/s12879-022-07169-w>

We report a clinically challenging and unusual case of *L. donovani* oral mucosal leishmaniasis. Israeli resident with a former travel to central and North Africa, with no documented or prior cutaneous lesions presented with oral lesions of the maxillary gingiva and the upper lip. A delay in diagnosis and treatment have led to progression of the maxillary gingival lesions towards the hard palate and the soft palate that could have potentially compromised the upper airway. This case highlights the importance of early diagnosis of leishmaniasis in patients with oral lesions and the laboratory workup necessary to appropriately characterize and treat the disease.

Antioxidant defence system as a rational target for Chagas disease and Leishmaniasis chemotherapy.

Santi, A., Murta/, S.

28-02-2022

Mem Inst Oswaldo Cruz

<https://pubmed.ncbi.nlm.nih.gov/35239945>

Chagas disease and leishmaniasis are neglected tropical diseases caused by the protozoan parasites *Trypanosoma cruzi* and *Leishmania* spp., respectively. They are among the most important parasitic diseases, affecting millions of people worldwide, being a considerable global challenge. However, there is no human vaccine available against *T. cruzi* and *Leishmania* infections, and their control is based mainly on chemotherapy. Treatments for Chagas disease and leishmaniasis have multiple limitations, mainly due to the high toxicity of the available drugs, long-term treatment protocols, and the occurrence of drug-resistant parasite strains. In the case of Chagas disease, there is still the problem of low cure rates in the chronic stage of the disease. Therefore, new therapeutic agents and novel targets for drug development are

urgently needed. Antioxidant defence in Trypanosomatidae is a potential target for chemotherapy because the organisms present a unique mechanism for trypanothione-dependent detoxification of peroxides, which differs from that found in vertebrates. Cellular thiol redox homeostasis is maintained by the biosynthesis and reduction of trypanothione, involving different enzymes that act in concert. This study provides an overview of the antioxidant defence focusing on iron superoxide dismutase A, trypanredoxin peroxidase, and ascorbate peroxidase and how the enzymes play an important role in the defence against oxidative stress and their involvement in drug resistance mechanisms in *T. cruzi* and *Leishmania* spp.

Centrin-deficient *Leishmania mexicana* confers protection against New World cutaneous leishmaniasis.

Volpedo, G., Pacheco-Fernandez, T., Holcomb, E., Zhang, W., Lypaczewski, P., Cox, B., Fultz, R., Mishan, C., Verma, C., Huston, R., Wharton, A., Dey, R., Karmakar, S., Oghumu, S., Hamano, S., Gannavaram, S., Nakhasi, H., Matlashewski, G., Satoskar, A.

02-03-2022

NPJ Vaccines

<https://doi.org/10.1038/s41541-022-00449-1>

Leishmaniasis is a neglected protozoan disease affecting over 12 million people globally with no approved vaccines for human use. New World cutaneous leishmaniasis (CL) caused by *L. mexicana* is characterized by the development of chronic non-healing skin lesions. Using the CRISPR/Cas9 technique, we have generated live attenuated centrin knockout *L. mexicana* (*LmexCen^{-/-}*) parasites. Centrin is a cytoskeletal protein important for cellular division in eukaryotes and, in *Leishmania*, is required only for intracellular amastigote replication. We have investigated the safety and immunogenicity characteristics of *LmexCen^{-/-}* parasites by evaluating their survival and the cytokine production in bone-marrow-derived macrophages (BMDMs) and dendritic cells (BMDCs) in vitro. Our data shows that *LmexCen^{-/-}* amastigotes present a growth defect, which results in significantly lower parasitic burdens and increased protective cytokine production in infected BMDMs and BMDCs, compared to the wild type (WT) parasites. We have also determined the safety and efficacy of *LmexCen^{-/-}* in vivo using experimental murine models of *L. mexicana*. We demonstrate that *LmexCen^{-/-}* parasites are safe and do not cause lesions in susceptible mouse models. Immunization with *LmexCen^{-/-}* is also efficacious against challenge with WT *L. mexicana* parasites in genetically different BALB/c and C57BL/6 mouse models. Vaccinated mice did not develop cutaneous lesions, displayed protective immunity, and showed significantly lower parasitic burdens at the infection site and draining lymph nodes compared to the control group. Overall, we demonstrate that *LmexCen^{-/-}* parasites are safe and efficacious against New World cutaneous leishmaniasis in pre-clinical models.

Signal peptide peptidase: A potential therapeutic target for parasitic and viral infections.

Schwake, C., Hyon, M., Chishti, A.

02-03-2022

Expert Opin Ther Targets

<https://doi.org/10.1080/14728222.2022.2047932>

Signal peptide peptidase (SPP) is a GxGD-type intramembrane-cleaving aspartyl protease responsible for clearing accumulating signal peptides in the endoplasmic reticulum. SPP is conserved among all kingdoms and is essential for maintaining cell homeostasis. Inhibition of SPP with selective inhibitors and the structurally similar HIV protease inhibitors results in signal peptide accumulation and subsequent cell death. Identification of SPP homologues in major human parasitic infections has opened a new therapeutic opportunity. Moreover, the essentiality of mammalian SPP-mediated viral protein processing during infection is emerging. This review introduces the discovery and biological function of human SPP enzymes and identify parasitic homologues as pharmacological targets of both SPP and HIV protease inhibitors. Later, the role of mammalian SPP during viral infection and how disruption of host SPP can be employed as a novel antiviral therapy are examined and discussed. Parasitic and viral infections cause severe health and economic burden, exacerbated by the lack of new therapeutics in the pipeline. SPP has been shown to be essential for malaria parasite growth and encouraging evidence in other parasites demonstrates broad essentiality of these proteases as therapeutic targets. As drug resistant parasite and viruses emerge, SPP inhibition will provide a new generation of compounds to counter the growing threat of antimicrobial resistance.

Fauna, Seasonal Activity, and Altitudinal Distribution of Phlebotomine Sand Flies (Diptera: Psychodidae) in Leishmaniasis Endemic Area, Aydın Mountains, and Surroundings in Western Turkey

Arserim, S., Mermer, A., Özbel, Y.

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Turkiye Parazitol Derg

<https://doi.org/10.4274/tpd.galenos.2022.35119>

Human and canine leishmaniasis (CanL) are endemic in Turkey, and cutaneous leishmaniasis (CL) is a primary public health problem among vector-borne diseases, with 1500-2000 autochthonous cases per year. In this study, we aimed to perform a comprehensive entomological survey, including the detection of sand fly fauna, seasonal activity, and altitudinal distribution, together with the ecological features of Aydın Mountains and their surroundings that are endemic areas for CL caused by *Leishmania tropica* and CanL caused by *L. infantum* MON-1. The survey was carried out from June 2009 to July 2010. Ten localities with different altitudes were selected. Sand fly collection was done every 15 days in July and August when sand flies are most active and every 30 days between September and June (14 months, 16 samplings) using CDC light traps and sticky traps. During the collection, the

temperature, humidity, and ecological and environmental features were recorded. Sand fly specimens were dissected and identified at species level using written keys. A total of 6712 sand fly specimens (3268 females and 3444 males) were collected from 10 localities throughout all study periods. Species identification revealed that nine and three species belonging to *Phlebotomus* (*P. major* s.l. 30.38%, *P. tobbi* 22.93%, *P. papatasi* 5.88%, *P. sergenti* s.l. 4.51%, *P. alexandri* 4.26%, *P. simici* 3.50%, *P. burneyi* 0.63%, *P. brevis* 0.45%, and *Transphlebotomus* spp. 0.28%) and *Sergentomyia* (*S. dentata* 23.17%, *S. minuta* 2.43%, and *S. antennata* 1.58%) were found, respectively. The seasonal activities of these 12 sand fly species were determined, and *P. major* s.l. and *P. tobbi*, which were probable vectors of VL and CanL, were present in the study area. *P. sergenti* s.l., a probable vector of CL, was also found in the region and was active for seven months between April and October. *P. sergenti* s.l. was found in the 400-600 m altitude in July, while *P. major* and *P. tobbi* were found in high densities in the 200-400 m altitude in September. Our results showed that leishmaniasis vectors are present in different altitudes in the Aydın mountains and surroundings. The findings revealed the time intervals of parasite transmission in the area and the period of applying protective measures, such as insecticide application.

Evaluation of Cases with Suspected Canine Leishmaniasis History: A Five-year Retrospective Study (2016-2021)

Pekağırbaş, M., Bakırcı, S., Bilgiç, H., Hacılarlıoğlu, S., Karagenc, T.

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Turkiye Parazit Derg

<https://doi.org/10.4274/tpd.galenos.2021.70299>

This study aimed to evaluate the polymerase chain reaction (PCR) and immunofluorescence antibody test (IFAT) results of suspected samples with canine leishmaniasis (CanL) that were sent to the Parasitology Department Laboratories of the Veterinary Faculty in Aydın Adnan Menderes University. The age, gender, and breed of the dogs to be evaluated for CanL were recorded, and IFAT was performed using 80 blood serum samples collected from them. Additionally, after the isolation of genomic DNA of 27 blood samples, PCR of these samples was performed using primers that amplify the 145 bp kDNA region of *Leishmania* species. Thirty-seven (46.25%) of the serum samples were seropositive in at least one dilution (1/64 or 1/128) according to IFAT. Five (18.5%) of the twenty-seven samples were positive for *Leishmania* DNA according to PCR. According to IFAT, 38.7% of male dogs and 59% of female dogs were positive. The highest number of seropositive samples were detected in dogs aged 3-5 years (11/27). Considering the zoonotic potential of leishmaniasis, which is considered endemic in the region, and the high positivity of the IFAT/PCR results, veterinarians should use advanced diagnostic methods, especially serological and molecular tests, in dogs with suspected CanL. The data obtained show that the risk of infection caused by *Leishmania* spp. is high in the region.

Therefore, it is important to routinely ensure the control of CanL to protect both human and animal health.

The Efficacy of Systemic Treatment for Leishmania tropica Cutaneous Leishmaniasis.

Solomon, M., Greenberger, S., Milner, M., Pavlotzky, F., Barzilai, A., Schwartz, E., Hadayer, N., Baum, S.

01-03-2022

Acta Derm Venereol

<https://doi.org/10.2340/actadv.v102.2079>

The effectiveness of systemic treatment for *Leishmania tropica* cutaneous leishmaniasis (CL) remains unclear. The purpose of the study is to evaluate the efficacy and safety of systemic treatments available against *L. tropica* CL. This retrospective study was performed in 114 patients. Systemic treatments included liposomal amphotericin B (L-AmB) and sodium stibogluconate (SSG). One hundred and fourteen patients underwent systemic treatment for *L. tropica* CL. Favorable treatment responses were recorded in 72.5% and 70.2% of the patients in the L-AmB and SSG groups, respectively; 25.3% and 46% of those in the L-AmB and SSG groups respectively, experienced at least one adverse effect. Lesions in cartilaginous areas were associated with higher treatment failure. Prior topical or systemic treatment increased the chance of future systemic treatment success. L-AmB was associated with a shorter IV treatment duration and a better safety profile. Thus, L-AmB is the treatment of choice for *L. tropica* CL.

Absence of DEATH kinesin is fatal for Leishmania mexicana amastigotes.

Al Kufi, S., Emmerson, J., Rosenqvist, H., Garcia, C., Rios-Szwed, D., Wiese, M.

28-02-2022

Sci Rep

<https://doi.org/10.1038/s41598-022-07412-z>

Kinesins are motor proteins present in organisms from protists to mammals playing important roles in cell division, intracellular organisation and flagellum formation and maintenance. *Leishmania mexicana* is a protozoan parasite of the order Kinetoplastida causing human cutaneous leishmaniasis. Kinetoplastida genome sequence analyses revealed a large number of kinesins showing sequence and structure homology to eukaryotic kinesins. Here, we investigate the *L. mexicana* kinesin LmxKIN29 (LmxM.29.0350), also called DEATH kinesin. The activated MAP kinase LmxMPK3, a kinase affecting flagellum length in *Leishmania*, is able to phosphorylate recombinant full length LmxKIN29 at serine 554. Insect promastigote LmxKIN29 *Leishmania* null mutants showed no obvious phenotype. However, in mouse infection experiments, the null mutants were unable to cause the disease, whereas LmxKIN29 add-backs and single allele knockouts caused footpad lesions. Localisation using promastigotes expressing GFP-tagged LmxKIN29 revealed that the kinesin is predominantly found in between the nucleus and the flagellar pocket, while in dividing cells the GFP-fusion

protein was found at the anterior and posterior ends of the cells indicating a role in cytokinesis. The inability to cause lesions in infected animals and the amino acid sequence divergence from mammalian kinesins suggests that LmxKIN29 is a potential drug target against leishmaniasis.

Functional Study of *Leishmania braziliensis* Protein Arginine Methyltransferases (PRMTs) Reveals That PRMT1 and PRMT5 Are Required for Macrophage Infection.

Lorenzon, L., Quilles, J., Campagnaro, G., Azevedo Orsine, L., Almeida, L., Veras, F., Miserani Magalhães, R., Alcoforado Diniz, J., Rodrigues Ferreira, T., Kaysel Cruz, A.

28-02-2022

ACS Infect Dis

<https://doi.org/10.1021/acscinfecdis.1c00509>

In trypanosomatids, regulation of gene expression occurs mainly at the posttranscriptional level, and RNA-binding proteins (RBPs) are key players in determining the fates of transcripts. RBPs are targets of protein arginine methyltransferases (PRMTs), which posttranslationally regulate the RNA-binding capacity and other RBP interactions by transferring methyl groups to arginine residues (R-methylation). Herein, we functionally characterized the five predicted PRMTs in *Leishmania braziliensis* by gene knockout and endogenous protein HA tagging using CRISPR/Cas9 gene editing. We report that R-methylation profiles vary among *Leishmania* species and across *L. braziliensis* lifecycle stages, with the peak PRMT expression occurring in promastigotes. A list of PRMT-interacting proteins was obtained in a single coimmunoprecipitation assay using HA-tagged PRMTs, suggesting a network of putative targets of PRMTs and cooperation between the R-methylation writers. Knockout of each *L. braziliensis* PRMT led to significant changes in global arginine methylation patterns without affecting cell viability. Deletion of either PRMT1 or PRMT3 disrupted most type I PRMT activity, resulting in a global increase in monomethyl arginine levels. Finally, we demonstrate that *L. braziliensis* PRMT1 and PRMT5 are required for efficient macrophage infection in vitro, and for axenic amastigote proliferation. The results indicate that R-methylation is modulated across lifecycle stages in *L. braziliensis* and show possible functional overlap and cooperation among the different PRMTs in targeting proteins. Overall, our data suggest important regulatory roles of these proteins throughout the *L. braziliensis* life cycle, showing that arginine methylation is important for parasite-host cell interactions.

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

Imran, M., Khan, S., Abida, ., Alshrari, A., Eltahir Mudawi, M., Alshammari, M., Harshan, A., Alshammari, N.

28-02-2022

Expert Opin Ther Pat

<https://doi.org/10.1080/13543776.2022.2045948>

: 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. : 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 December 31, 2021. : 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.

N⁶-modification of 7-Deazapurine nucleoside analogues as Anti-Trypanosoma cruzi and anti-Leishmania agents: Structure-activity relationship exploration and In vivo evaluation.

Lin, C., Jaén Batista, D., Mazzeti, A., Donola Girão, R., de Oliveira, G., Karalic, I., Hulpia, F., Soeiro, M., Maes, L., Caljon, G., Van Calenbergh, S.

31-01-2022

Eur J Med Chem

<https://pubmed.ncbi.nlm.nih.gov/35144125>

Chagas disease and leishmaniasis are two poverty-related neglected tropical diseases that cause high mortality and morbidity. Current treatments suffer from severe limitations and novel, safer and more effective drugs are urgently needed. Both *Trypanosoma cruzi* and *Leishmania* are auxotrophic for purines and absolutely depend on uptake and assimilation of host purines. This led us to successfully explore purine nucleoside analogues as chemotherapeutic agents against these and other kinetoplastid infections. This study extensively explored the modification of the 6-amino group of tubercidin, a natural product with trypanocidal activity but unacceptable toxicity for clinical use. We found that mono-substitution of the amine with short alkyls elicits potent and selective antitrypanosomal and antileishmanial activity. The methyl analogue 15 displayed the best in vitro activity against both *T. cruzi* and *L. infantum* and high selectivity versus host cells. Oral administration for five consecutive days in an acute Chagas disease mouse model resulted in significantly reduced peak parasitemia levels (75, 89 and 96% with 12.5, 25 and 50 mg/kg/day, respectively). as well as increased animal survival rates with the lower doses (83 and 67% for 12.5 and 25 mg/kg/day, respectively).

Citizen science set in motion: DIY light traps for phlebotomine sand flies.

Gálvez, R., de Felipe, M., Yebes, F.

25-01-2022

Prev Vet Med

<https://pubmed.ncbi.nlm.nih.gov/35123171>

Phlebotomine sand flies are vectors of various diseases such as leishmaniasis making them a public health concern worldwide. To increase the tools available for the study of sand flies, we developed do it yourself (DIY) light traps made mainly from recycled materials and tested their effectiveness in the field. This new model is named Flebocollect light trap. In this report we describe how the DIY light traps are prepared and illustrate the process with a short video. Lowering costs makes this resource available for citizen science and educational projects, and for research groups with a low budget such as those in developing countries. Our preliminary results showed a capture rate increase of 37 % of DIY light traps over commercial CDC, although no statistical evidence has been obtained.

A Historic Review of the Role of CD4+ T-Cell Subsets in Development of the Immune Responses against Cutaneous and Visceral Leishmaniasis

Alimohmmadian, M., Ajdary, S., Bahrami, F.

01-03-2022

Iran Biomed J

<https://doi.org/10.52547/ibj.26.2.99>

The heterogeneity of CD4+ T cells has been investigated since the late 1970s, when their Th1 and Th2 subsets were coined. Later studies on the cutaneous form of the Leishmaniasis were focused on the experimental models of *Leishmania major* infection using the susceptible BALB/c and the resistant C57BL/6 mice. At the early 21st century, the regulatory T-cells subpopulation was introduced and its role in concomitant immunity, responsible for lifelong resistance of the host to the reinfection was proposed. Subsequent studies, mainly focused on the visceral form of the infection pointed to the role of IL-17, produced by Th17 subset of CD4+ T cells that along the neutrophils were shown to have important yet equivocal functions in protection against or exacerbation of the infection. Altogether, the current knowledge indicates that the above four subsets could orchestrate the immune, the regulatory and the inflammatory responses of the host against different forms of leishmaniasis.

Positivity, diagnosis and treatment follow-up of cutaneous leishmaniasis in war-affected areas of Bajaur, Pakistan.

Arif, M., Kalsoom, ., Shah, A., Badshah, M., Hasan, F., Rehman, A., Khan, S.

25-01-2022

Parasitol Res

<https://doi.org/10.1007/s00436-022-07438-2>

This study was conducted to explore the frequency of positivity of cutaneous leishmaniasis (CL) in the tribal district Bajaur located near the Pak-Afghan border. The present study was conducted at the Leishmaniasis Center of Headquarter Hospital Khar District Bajaur, Pakistan. In total, 646 patients were recruited and included in the study after ethical approval and consent from the patients. CL was confirmed by taking blood samples from the sides of the lesion and observing them under a microscope using Giemsa staining. Information about demographic factors was collected from the study participants with a questionnaire and analyzed by SPSS. It was found that 73.8% of suspected patients were positive and 26.2% were negative for CL. There were 51.9% male and 48.1% female patients. The most frequently affected site was the face (42.6%), and most of the patients (85.8%) had only one lesion. The positivity of CL was higher among those under age 15 years. The area of most positivity, with 45.2% of the cases, was Tehsil Mamund. Most of the patients (46.6%) lived in stone houses, with 98.6% of patients having domestic animals in their houses. Approximately 198 patients were treated with intramuscular and intralesional injections of meglumine antimoniate, and their weekly follow-up revealed that 48% of patients recovered, while the remaining patients left the course of treatment at different stages of therapy. The positivity of CL is high in this area and is confirmed by the detection of *Leishmania amastigotes* in the blood collected from their lesions. Socioeconomic factors are the main underlying causes of the rapid spread of this disease and meglumine antimoniate is an effective drug.

Molecular identification of *Leishmania RNA virus* in cutaneous leishmaniasis patients and rodent reservoirs in Isfahan province, Iran.

Farrokhi-Karibozorg, M., Ghayour-Najafabadi, Z., Hejazi, S., Ataei-Pirkooch, A., Mohebali, M., Teimouri, P., Hajjarian, H.

20-01-2022

Infect Genet Evol

<https://pubmed.ncbi.nlm.nih.gov/35066166>

Leishmania RNA virus (LRV) is a double-strand RNA virus that was first detected in members of the *Leishmania viannia* in the New World. The present study aimed to investigate the presence of LRV in the *Leishmania* species isolated from cutaneous leishmaniasis (CL) patients and rodents as reservoirs in Isfahan province an old zoonotic CL focus, center of Iran. Totally, 85 samples were collected from CL patients (n = 80) and rodent reservoirs (n = 5) from different regions of Isfahan province. Species identification was determined using the PCR-RFLP method. Viral dsRNA was extracted and for observation of 5.3 kb dsRNA on an agarose gel. The presence of LRV was surveyed using the Semi-nested PCR method. For phylogenetic analyzes, 6 samples of 13 isolates were sequenced and a phylogenetic tree was drawn by MEGA7 version 7.0.26. Of 80 *Leishmania* isolates recovered from the patients with CL, 79 and only one were identified as *L. major* and *L. tropica*, respectively. Also, the PCR assays detected four *L. major* and one *L. turanica* in five assessed *Rhombomys opimus* as the

rodent reservoirs. LRV was detected only in *Leishmania* species isolated from 13 species of 85 (15.3%) CL including (*L. major*, n = 12) and (*L. tropica*, n = 1). Phylogenetic analysis showed that they were belonged to LRV2 and had the highest similarity with Iranian reference LRV2 in GenBank. Our results showed that the LRV2 was present in cutaneous *Leishmania* species in Isfahan province is the most historical and touristic province of Iran. In the study LRV was not reported from rodent reservoirs, it may be due to the small sample size. Phylogenetic analysis of current sequences demonstrated that these isolates belong to the registered LRV2 of the Old World.

Leishmaniosis caused by *Leishmania infantum* in ferrets: Update review.

Villanueva-Saz, S., Giner, J., Marteles, D., Verde, M., Yzuel, A., Riera, C., Fisa, R., Alcover, M., Fernández, A.

27-12-2021

Vet Anim Sci

<https://doi.org/10.1016/j.vas.2021.100229>

Leishmaniosis in domestic ferrets (*Mustela putorius furo*) is a disease caused by *Leishmania infantum*, a parasite transmitted through the bite of an infected female phlebotomine sand fly. Among vertebrates, the dog is the primary domestic reservoir of the parasite; however, other domestic animals can be implicated such as cats. The first description of a clinical case of leishmaniosis in domestic ferrets was reported recently. As a result, new knowledge has been published including empirically based treatment protocols, confirmatory techniques to detect the presence of the parasite infection and seasonal variation in the antibodies against *Leishmania* in apparently healthy domestic ferrets. The most common clinical signs observed are enlargement of peripheral lymph nodes and skin lesions such as papular and/or ulcerative dermatitis. Additionally, the most frequent laboratory alterations seen are hyperproteinaemia with hyperglobulinaemia and biochemical analytes alterations depending on the affected tissue. Two different therapeutic protocols have been described to treat domestic ferrets with leishmaniosis: meglumine antimoniate plus allopurinol protocol or miltefosine plus allopurinol protocol. These treatment protocols seemed to be able to control the *Leishmania* infection, although the presence of xanthinuria could be detected. The susceptibility of domestic ferrets to *Leishmania infantum*, the clinical picture, treatment of infected animals and prevention are poorly understood, due to the scarcity of recent description in the literature. Different proposed diagnostic algorithms have been included for domestic ferrets with suspected leishmaniosis, clinically healthy domestic ferrets and animals as blood donors. In this sense, the present review provides updated data on scientific knowledge of leishmaniosis in ferrets.

Human genetic polymorphism and Leishmaniasis.

Bharati, K.

04-01-2022

Infect Genet Evol

<https://pubmed.ncbi.nlm.nih.gov/34990851>

Leishmaniasis is a disease of the subtropical and tropical spheres of the earth and has various clinical manifestations. The different form of leishmaniasis includes cutaneous leishmaniasis, mucocutaneous leishmaniasis, most lethal visceral leishmaniasis and PKDL form. These different forms depend on many factors such as parasite and vector species, geographical, environmental conditions and population ethnicity. Host genetic factors have been widely investigated for their role in developing the disease in various infections. There are several reports on associations or resistance between candidate gene polymorphisms and the risk and outcome of *Leishmania* infection. Polymorphism in genes involved in both innate and adaptive immune systems, as well as genes of metabolic processes contributes to disease manifestation. The wide availability and advancement of molecular techniques permits to exploration of hereditary factors related to leishmaniasis. Many candidate gene studies were conducted on family-based and population to identify novel biomarkers for understanding disease pathogenesis pathways and possible drug targets. This comprehensive review presents an update on various human genes polymorphism that influence the outcome of different forms of *Leishmania* infection in endemic regions of the world. Various electronic databases were searched systematically for relevant publications and thoroughly analyzed. Most of the candidate gene studies were found with discrepancies in findings. Genetic and functional studies with adequate power are needed to validate the contribution of host genes in susceptibility or resistance towards *Leishmania* infection and understanding pathogenesis.

The involvement of host circadian clocks in the regulation of the immune response to parasitic infections in mammals.

Carvalho Cabral, P., Tekade, K., Stegeman, S., Olivier, M., Cermakian, N.

11-01-2022

Parasite Immunol

<https://doi.org/10.1111/pim.12903>

Circadian rhythms are recurring variations of physiology with a period of ~24 h, generated by circadian clocks located throughout the body. Studies have shown a circadian regulation of many aspects of immunity. Immune cells have intrinsic clock mechanisms, and innate and adaptive immune responses - such as leukocyte migration, magnitude of inflammation, cytokine production and cell differentiation - are under circadian control. This circadian regulation has consequences for infections including parasitic infections. In the context of *Leishmania* infection, the circadian clock within host immune cells modulates the magnitude of the infection and the inflammatory response triggered by the parasite. As for malaria, rhythms within the immune system were shown to impact the developmental cycles of *Plasmodium* parasites within red blood cells. Further, host circadian rhythms impact infections by multicellular parasites; for example, infection with helminth *Trichuris muris* shows different kinetics of worm expulsion depending on time of day of infection, a variation that

depends on the dendritic cell clock. Although the research on the circadian control of immunity in the context of parasitic infections is in its infancy, the research reviewed here suggests a crucial involvement of host circadian rhythms in immunity on the development and progression of parasitic infections.

Eugenol carbonate activity against *Plasmodium falciparum*, *Leishmania braziliensis*, and *Trypanosoma cruzi*.

Clemente, C., Pineda, T., Yepes, L., Upegui, Y., Allemandi, D., Robledo, S., Ravetti, S.

26-12-2021

Arch Pharm (Weinheim)

<https://doi.org/10.1002/ardp.202100432>

Neglected tropical diseases are a major health problem throughout the world, and there are few effective and safe drugs. In this study, we report the design and synthesis of a novel series of carbonates of eugenol using different aliphatic alcohols and N,N-carbonyldiimidazole. Spectroscopic techniques, including ^1H nuclear magnetic resonance (NMR), ^{13}C NMR, Fourier transform infrared, and high-resolution mass spectrometry, were used to confirm the structures of the synthesized compounds. In vitro and in silico studies of prodrugs of eugenol were performed to determine their antiparasitic, trypanocidal, and leishmanicidal activities, and also their cytotoxicity. Compounds were highly active against *Leishmania braziliensis* and *Plasmodium falciparum*, whereas the activity shown for *Trypanosoma cruzi* was moderate. Molecular docking was used to determine a possible mode of action of eugenol against the dihydroorotate dehydrogenase of the three parasites (TcDHODH, LbDHODH, and PfdHODH). Notably, the docking results showed that eugenol not only has binding energy similar to that of the natural substrate (-7.2 and -7.1, respectively) but also has interactions with relevant biological residues of PfdHODH. This result indicates that eugenol could act as a substrate for PfdHODH in the pyrimidine biosynthesis pathway of *P. falciparum*. In conclusion, the combination of certain aliphatic alcohols and eugenol through a carbonate bond could significantly increase the antiparasitic activity of this class of compounds, which merits further studies.

Plasma membrane rigidity effects of 4-hydroxy-2-nonenal in *Leishmania*, erythrocyte and macrophage.

Alonso, L., Menegatti, R., Dorta, M., Alonso, A.

09-12-2021

Toxicol In Vitro

<https://pubmed.ncbi.nlm.nih.gov/34896601>

4-hydroxy-2-nonenal (HNE) is a reactive aldehyde produced by cells under conditions of oxidative stress, which has been shown to react with proteins and phosphatidylethanolamine in biological membranes. Using electron paramagnetic resonance (EPR) spectroscopy of a spin label it was demonstrated that 2 h of treatment with HNE causes membrane rigidity in

promastigotes of *Leishmania (L.) amazonensis*, J774.A1 macrophages and erythrocytes. Remarkable fluidity-reducing effects on the parasite membrane were observed at HNE concentrations approximately 4-fold lower than in the case of erythrocyte and macrophage membranes. Autofluorescence of the parasites in PBS suspension (1×10^7 cell/mL) with excitation at 354 nm showed a linear increase of intensity in the range of 400 to 600 nm over 3 h after treatment with 30 μM HNE. Parasite ghosts prepared after this period of HNE treatment showed a high degree of membrane rigidity. Bovine serum albumin (BSA) in PBS treated with HNE for 2 h showed an increase in molecular dynamics and suffered a decrease in its ability to bind a lipid probe. In addition, the antiproliferative activity of *L. amazonensis* promastigotes, macrophage cytotoxicity and hemolytic potential were assessed for HNE. An IC_{50} of 24 μM was found, which was a concentration > 10 times lower than the cytotoxic and hemolytic concentrations of HNE. These results indicate that the action of HNE has high selectivity indices for the parasite as opposed to the macrophage and erythrocyte.

Nonstandard RNA/RNA interactions likely enhance folding and stability of segmented ribosomes.

Rivas, M., Fox, G.

07-12-2021

RNA

<https://doi.org/10.1261/rna.079006.121>

The ribosome is the molecular factory that catalyzes all coded protein synthesis in extant organisms. Eukaryotic ribosomes are typically assembled out of four rRNAs; namely, 5S, 5.8S, 18S, and 28S. However, the 28S rRNA of some trypanosomatid organisms has been found to be segmented into six independent rRNAs of different sizes. The two largest segments have multiple sites where they jointly form stems comprised of standard base pairs that can hold them together. However, such regions of interaction are not observed among the four smaller RNAs. Early reports suggested that trypanosomatid segmented ribosome assembly was essentially achieved thanks to their association with rProteins. However, examination of cryo-EM ribosomal structures from *Trypanosoma brucei*, *Leishmania donovani*, and *Trypanosoma cruzi* reveals several long-range nonstandard RNA/RNA interactions. Most of these interactions are clusters of individual hydrogen bonds and so are not readily predictable. However, taken as a whole, they represent significant stabilizing energy that likely facilitates rRNA assembly and the overall stability of the segmented ribosomes. In the context of origin of life studies, the current results provide a better understanding of the true nature of RNA sequence space and what might be possible without an RNA replicase.

Laboratory evidence that dinotefuran, pyriproxyfen and permethrin combination abrogates *Leishmania infantum* transmissibility by sick dogs.

Bongiorno, G., Bosco, A., Bianchi, R., Rinaldi, L., Foglia Manzillo, V., Gizzarelli, M., Maurelli, M., Giaquinto, D., El

Houda Ben Fayala, N., Varloud, M., Crippa, A., Oliva, G., Gradoni, L., Cringoli, G.

01-11-2021

Med Vet Entomol

<https://doi.org/10.1111/mve.12553>

Dogs are reservoir hosts of leishmaniasis caused by *Leishmania infantum* and transmitted by phlebotomine vectors. The effect of dinotefuran, pyriproxyfen and permethrin spot-on solution (Vectra®3D, Ceva Santé Animale, Libourne, France) on *Leishmania* transmissibility by naturally infected dogs via reared *Phlebotomus perniciosus*, was assessed. Dogs affected by leishmaniasis were submitted to xenodiagnosis and 6 infecting >10% of insects were treated topically on day 0. Antifeeding, insecticidal and anti-transmissibility effects were evaluated through xenodiagnoses performed on days 1, 7 and 28, using individual pre-treatment parameters as control. Feeding and mortality rates were assessed at 24h, whereas promastigote infection, maturation and burden were assessed up to 96h post blood meal (potentially infectious rate). On day 1, the anti-feeding efficacy was >95% in 4 dogs, insecticidal efficacy 100% in 4 dogs, and anti-transmissibility effect 100% in 6 dogs. Efficacy rates recorded on day 7 were very similar to day 1. On day 28, anti-feeding and insecticidal efficacy values were much broader, ranging 32.6-100% and 7.7-94.4%, respectively. Potentially infectious insects were recorded from two dogs, with sharp decrease in transmissibility rate as compared with pre-treatment condition. Altogether, Vectra®3D abrogated by >98% the potential *Leishmania* transmissibility by the examined pool of infected dogs over 1 month.

Going ballistic: *Leishmania* nuclear subversion of host cell plasticity.

Lecoœur, H., Prina, E., Gutiérrez-Sánchez, M., Späth, G.

16-10-2021

Trends Parasitol

<https://pubmed.ncbi.nlm.nih.gov/34666937>

Intracellular parasites have evolved intricate strategies to subvert host cell functions for their own survival. These strategies are particularly damaging to the host if the infection involves immune cells, as illustrated by protozoan parasites of the genus *Leishmania* that thrive inside mononuclear phagocytic cells, causing devastating immunopathologies. While the impact of *Leishmania* infection on host cell phenotype and functions has been well documented, the regulatory mechanisms underlying host cell subversion were only recently investigated. Here we summarize the current knowledge on how *Leishmania* infection affects host nuclear activities and propose thought-provoking new concepts on the reciprocal relationship between epigenetic and transcriptional regulation in host cell phenotypic plasticity, its potential subversion by the intracellular parasite, and its relevance for host-directed therapy.

Cross-reactive, natural IgG recognizing *L. major* promote parasite internalization by dendritic cells and promote protective immunity.

Dermicik, F., Lopez Kostka, S., Tenzer, S., Waisman, A., Von Stebut, E.

04-10-2021

J Mol Med (Berl)

<https://doi.org/10.1007/s00109-021-02137-4>

In cutaneous leishmaniasis, infection of dendritic cells (DC) is essential for generation of T cell-dependent protective immunity. DC acquires *Leishmania major* through Fc receptor (FcR)-mediated uptake of complexes comprising antibodies bound to parasites. We now assessed the development of the initial B cell and DC response to the parasite itself and if natural IgG play a role. *L. major* parasites display large numbers of phospholipids on their surface. Parasites were opsonized with normal mouse serum (NMS), or serum containing anti-phospholipid IgG (PL). We found that *L. major* bound to PL which significantly enhanced parasite phagocytosis by DC as compared to NMS. Similar results were obtained with cross-reactive human PL antibodies using myeloid primary human DC. In addition, mice infected with PL-opsonized parasites showed significantly improved disease outcome compared to mice infected with NMS-opsonized parasites. Finally, IgMi mice, which produce membrane-bound IgM only and no secreted antibodies, displayed increased susceptibility to infection as compared to wild types. Interestingly, once NMS was administered to IgMi mice, their phenotype was normalized to that of wild types. Upon incubation with IgG-opsonized parasite (IgG derived from infected mice or using PL antibodies), also the IgMi mice were able to show superior immunity. Our findings suggest that "natural" cross-reactive antibodies (e.g., anti-PL Ab) in NMS bind to pathogens to facilitate phagocytosis, which leads to induction of protective immunity via preferential DC infection. Prior *L. major*-specific B cell-priming does not seem to be absolutely required to facilitate clearance of this important human pathogen in vivo. KEY MESSAGES: We found that anti-phospholipid (anti-PL) antibodies enhance phagocytosis of *L. major* by DCs. We also found that normal mouse sera have natural antibodies that can imitate PL specific antibodies. Using different genetically modified mice, we found that these antibodies can be IgG, not only IgM.

Elevated and sustained anti-feeding effect of Scalibor® deltamethrin collar against the sand fly *Phlebotomus perniciosus* in dogs confirmed for 1 year following treatment.

Evans, A., Bongiorno, G., Fourie, J., Lekouch, N., Bianchi, R., Khoury, C., Thomas, E., Chiummo, R., Gradoni, L.

27-08-2021

Med Vet Entomol

<https://doi.org/10.1111/mve.12545>

Dogs are reservoir hosts for *Leishmania infantum*, a protozoan parasite transmitted by phlebotomine sand flies. The anti-feeding and fast-killing efficacy of Scalibor® deltamethrin collars against experimental *Phlebotomus perniciosus*

challenges on dogs was determined over 1 year. Two groups of 8 dogs each were fitted with placebo (control) or deltamethrin collars (treated) on Day 0 and exposed to sand flies approximately every 28 days up to Day 364. After each exposure, anti-feeding and fast-killing efficacy rates were determined by comparing blood-fed or live insects, respectively, in the treated vs. the control group. Blood-fed and live sand flies were significantly less in treated dogs as compared to control dogs at each assessment. The anti-feeding efficacy rate exceeded 90% except on Day 337 (89%) but increased again (96%) on Day 364. Fast killing efficacy was <74% over the study when considering all flies. However, this value increased cumulatively to 98% when only blood-fed flies were compared between groups. Scalibor® collars are highly effective at preventing *P. perniciosus* blood-feeding and in fast-killing flies taking a blood meal for up to 1 year after application. These strong and long-lasting effects are an important strategic component for *L. infantum* transmission control.

Pentalinosterol, a Phytosterol from *Pentalinon andrieuxii*, is Immunomodulatory through Phospholipase A₂ in Macrophages toward its Antileishmanial Action.

Varikuti, S., Shelton, A., Kotha, S., Gurney, T., Gupta, G., Hund, T., Fuchs, J., Kinghorn, A., Srivastava, N., Satoskar, A., Parinandi, N.

13-08-2021

Cell Biochem Biophys

<https://doi.org/10.1007/s12013-021-01030-8>

Our earlier in vitro and in vivo studies have revealed that the phytosterol, pentalinosterol (cholest-4,20,24-trien-3-one) (PEN), isolated from the roots of *Pentalinon andrieuxii*, possesses immunomodulatory properties in macrophages and dendritic cells. Leishmaniasis, caused by the infection of *Leishmania* spp. (a protozoan parasite), is emerging as the second-leading cause of mortality among the tropical diseases and there is an unmet need for a pharmacological intervention of leishmaniasis. Given the beneficial immunomodulatory actions and lipophilic properties of PEN, the objective of this study was to elucidate the mechanism(s) of action of the immunomodulatory action(s) of PEN in macrophages through the modulation of phospholipase A₂ (PLA₂) activity that might be crucial in the antileishmanial action of PEN. Therefore, in this study, we investigated whether PEN would modulate the activity of PLA₂ in RAW 264.7 macrophages and mouse bone marrow-derived primary macrophages (BMDMs) in vitro and further determined how the upstream PLA₂ activation would regulate the downstream cytokine release in the macrophages. Our current results demonstrated that (i) PEN induced PLA₂ activation (arachidonic acid release) in a dose- and time-dependent manner that was regulated upstream by the mitogen-activated protein kinases (MAPKs); (ii) the PEN-induced activation of PLA₂ was attenuated by the cPLA₂-specific pharmacological inhibitors; and (iii) the cPLA₂-specific pharmacological inhibitors attenuated the release of inflammatory cytokines from the macrophages. For the first time, our current study demonstrated that PEN exhibited its

immunomodulatory actions through the activation of cPLA₂ in the macrophages, which potentially could be used in the development of a pharmacological intervention against leishmaniasis.

CYSTICERCOSIS

Isolated Intramuscular Cysticercosis in Children: A Case Report

Kumar H C, K., Narayana, P., Kumar, K.

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Turkiye Parazitoloj Derg

<https://doi.org/10.4274/tpd.galenos.2020.6613>

Human cysticercosis is an emerging infection caused by the larvae of *Taenia solium* (*Cysticercus cellulosae*). The most common sites for cysticercosis are the central nervous system, subcutaneous tissues, eyes, and muscles. Isolated intramuscular cysticercosis without brain involvement is rare and only a few reports are available in children. Here, we report two children with isolated intramuscular cysticercosis who presented with the swellings that were diagnosed by ultrasonography and fine-needle aspiration cytology. Both of them responded well to steroids and albendazole treatment, showing a complete resolution of the swelling.

On pig *Taenia solium/asiatica* cysticercosis in India-Comment on 'Quantitative risk assessment of human *Taenia solium* exposure from consuming pork produced in Punjab, India'.

Galán-Puchades, M., Fuentes, M.

03-01-2022

Zoonoses Public Health

<https://doi.org/10.1111/zph.12906>

Cysticercosis in ophthalmology.

Pujari, A., Bhaskaran, K., Modaboyina, S., Das, D., Saluja, G., Samdani, A., Singh, P., Bajaj, M., Sharma, N.

30-07-2021

Surv Ophthalmol

<https://pubmed.ncbi.nlm.nih.gov/34339720>

Cysticercosis is caused by *Taenia solium*, a cestode or tapeworm that preferentially affects the subcutaneous tissue, brain, muscle, and the eye. It is traditionally a disease of low socioeconomic regions, but large-scale population migration has made it a matter of global concern. Its ocular invasion is a potentially blinding disease. In the last two decades, there has been considerable discussion of cysticercosis; however, most comes from a limited number of case observations. Thus, to overcome this limitation, we summarize and analyze twenty

years of medical literature (from 2000 to 2020) on cysticercosis in ophthalmology.

DRACUNCULOSE

Investigating Flubendazole as an Anthelmintic Treatment for Guinea Worm (*Dracunculus medinensis*): Clinical Trials in Laboratory-Reared Ferrets and Domestic Dogs in Chad.

Cleveland, C., Garrett, K., Box, E., Thompson, A., Haynes, E., Elder, D., Richards, R., Majewska, A., Guagliardo, S., Wiegand, R., Bryan li, J., Torres-Velez, F., Unterwegner, K., Romero, M., Zirimwabagabo, H., Sidouin, M., Oaukou, P., Ada, M., Ngandolo, B., Mackenzie, C., Geary, T., Weiss, A., Yabsley, M.

28-02-2022

Am J Trop Med Hyg

<https://doi.org/10.4269/ajtmh.21-1222>

Dracunculus medinensis (Guinea worm [GW]), a zoonotic nematode targeted for eradication, has been managed using interventions aimed at humans; however, increases in domestic dog GW infections highlight the need for novel approaches. We conducted two clinical trials evaluating the efficacy of subcutaneously injected flubendazole (FBZ) as a treatment of GW infection. The first trial was conducted administering FBZ to experimentally infected ferrets; the second trial involved administering FBZ or a placebo to domestic dogs in the Republic of Tchad (Chad). We found contrasting results between the two trials. When adult gravid female GW were recovered from ferrets treated with FBZ, larvae presented in poor condition, with low to no motility, and an inability to infect copepods. Histopathology results indicated a disruption to morulae development within uteri of worms from treated animals. Results from the trial in Chadian dogs failed to indicate significant treatment of or prevention against GW infection. However, the difference in treatment intervals (1 month for ferrets and 6 months for dogs) or the timing of treatment (ferrets were treated later in the GW life-cycle than dogs) could explain different responses to the subcutaneous FBZ injections. Both trials provided valuable data guiding the use of FBZ in future trials (such as decreasing treatment intervals or increasing the dose of FBZ in dogs to increase exposure), and highlighted important lessons learned during the implementation of a field-based, double-blinded randomized control trial in Chadian dogs.

Seasonal fishery facilitates a novel transmission pathway in an emerging animal reservoir of Guinea worm.

Goodwin, C., Léchenne, M., Wilson-Aggarwal, J., Koumetio, S., Swan, G., Moundai, T., Ozella, L., McDonald, R.

14-12-2021

Curr Biol

<https://pubmed.ncbi.nlm.nih.gov/34910949>

Exploitation of natural resources is a driver of human infectious disease emergence. The emergence of animal reservoirs of Guinea worm *Dracunculus medinensis*, particularly in domestic dogs *Canis familiaris*, has become the major impediment to global eradication of this human disease. 93% of all Guinea worms detected worldwide in 2020 were in dogs in Chad. Novel, non-classical pathways for transmission of Guinea worm in dogs, involving consumption of fish, have been hypothesized to support the maintenance of this animal reservoir. We quantified and analyzed variation in Guinea worm emergence in dogs in Chad, across three climatic seasons, in multiple villages and districts. We applied forensic stable isotope analyses to quantify dietary variation within and among dogs and GPS tracking to characterize their spatial ecology. At the end of the hot-dry season and beginning of the wet season, when fishing by people is most intensive, Guinea worm emergence rates in dogs were highest, dogs ate most fish, and fish consumption was most closely associated with disease. Consumption of fish by dogs enables a non-classical transmission pathway for Guinea worm in Chad. Seasonal fisheries and the facilitation of dogs eating fish are likely contributing to disease persistence and to this key impediment to human disease eradication. Interrelated natural resource use, climatic variation, companion animal ecology, and human health highlight the indispensability of One Health approaches to the challenges of eradicating Guinea worm and other zoonotic diseases.

ECHINOCOCCOSE

Echinococcosis in a non-endemic country - 20-years' surgical experience from a Norwegian tertiary referral Centre.

Yaqub, S., Jensenius, M., Heieren, O., Drolsum, A., Pettersen, F., Labori, K.

04-03-2022

Scand J Gastroenterol

<https://doi.org/10.1080/00365521.2022.2046846>

In Scandinavia, the incidence of cystic echinococcosis (CE) and alveolar echinococcosis (AE) is low and almost exclusively an imported disease following the trends of immigration. The aim of the study was to review available data on clinical management and outcome for patients treated at Oslo University Hospital, a referral centre for echinococcosis in Norway, with special emphasis on surgical treatment. All patients admitted with echinococcosis between January 2000 and December 2020 were identified. Medical records were reviewed retrospectively concerning patient demographics, treatment strategy, surgical procedures, complications and outcomes. A total of 92 patients with median age 37 years (range 4-85) were identified. Sixty-eight patients (74%) were

symptomatic. All patients, except for two, were immigrants to Norway and born in endemic areas. Ninety patients were diagnosed with CE and two with AE. Location of the cysts was most commonly in the liver (86%) followed by peritoneum, lungs, and spleen. All patients with active cysts were treated with albendazole. Surgical treatment was performed in 51 (56%) patients. The most common reason for abstaining from surgical treatment was that the diagnostic work-up revealed inactive cysts or interventional radiology was performed. Of the 51 patients who underwent surgery, a radical procedure was performed in 32 (64%) cases, a conservative procedure in 12 (24%), and a combination in six (12%). Clavien Dindo grade ≥ 3 complications occurred in 30%, and 90-day mortality was 2%. Bile leakage occurred in seven patients and was treated successfully with endoscopic retrograde cholangiopancreatography with biliary stent placement in all patients. In a low-endemic area like Norway, management of echinococcus includes medical therapy, surgery, and/or interventional radiology. Surgical intervention seems to be effective, and is associated with acceptable morbidity rates.

Zoonotic Pathogens in Eurasian Beavers (*Castor fiber*) in the Netherlands.

Maas, M., Glorie, J., Dam-Deisz, C., de Vries, A., Franssen, F., Jaarsma, R., Hengeveld, P., Dierikx, C., van der Giessen, J., Opsteegh, M.

04-03-2022

J Wildl Dis

<https://doi.org/10.7589/JWD-D-21-00097>

Successful repopulation programs of Eurasian beavers (*Castor fiber*) have resulted in an increase in beaver populations throughout Europe. This may be of public health relevance because beavers can host multiple zoonotic pathogens. From March 2018 to March 2020, opportunistic testing of dead beavers was performed for hepatitis E virus, orthohantavirus, *Anaplasma phagocytophilum*, *Bartonella* spp., extended-spectrum-beta-lactamase or AmpC (ESBL/AmpC)-producing Enterobacteriaceae, *Francisella tularensis*, *Leptospira* spp., *Neoehrlichia mikurensis*, *Babesia* spp., *Echinococcus multilocularis*, *Toxoplasma gondii*, and *Trichinella* spp. From the 24 beavers collected, three zoonotic pathogens were detected. One beaver was positive for *T. gondii*, one was positive for ESBL/AmpC-producing Enterobacteriaceae, and one was positive for *N. mikurensis*. The latter finding indicates that beavers can be bitten by *Ixodes ricinus* and be exposed to tick-borne pathogens. The detected ESBL/AmpC-gene was blaCMY-2 in an *Escherichia coli* ST6599. The findings suggest that the role of beavers in the spread of zoonotic diseases in the Netherlands is currently limited.

Chromosome-scale *Echinococcus granulosus* (genotype G1) genome reveals the Eg95 gene family and conservation of the EG95-vaccine molecule.

Korhonen, P., Kinkar, L., Young, N., Cai, H., Lightowlers, M., Gauci, C., Jabbar, A., Chang, B., Wang, T., Hofmann, A., Koehler, A., Li, J., Li, J., Wang, D., Yin, J., Yang, H., Jenkins,

D., Saarma, U., Laurimäe, T., Rostami-Nejad, M., Irshadullah, M., Mirhendi, H., Sharbatkhori, M., Ponce-Gordo, F., Simsek, S., Casulli, A., Zait, H., Atoyian, H., de la Rue, M., Romig, T., Wassermann, M., Aghayan, S., Gevorgyan, H., Yang, B., Gasser, R.

03-03-2022

Commun Biol

<https://doi.org/10.1038/s42003-022-03125-1>

Cystic echinococcosis is a socioeconomically important parasitic disease caused by the larval stage of the canid tapeworm *Echinococcus granulosus*, afflicting millions of humans and animals worldwide. The development of a vaccine (called EG95) has been the most notable translational advance in the fight against this disease in animals. However, almost nothing is known about the genomic organisation/location of the family of genes encoding EG95 and related molecules, the extent of their conservation or their functions. The lack of a complete reference genome for *E. granulosus* genotype G1 has been a major obstacle to addressing these areas. Here, we assembled a chromosomal-scale genome for this genotype by scaffolding to a high quality genome for the congener *E. multilocularis*, localised Eg95 gene family members in this genome, and evaluated the conservation of the EG95 vaccine molecule. These results have marked implications for future explorations of aspects such as developmentally-regulated gene transcription/expression (using replicate samples) for all *E. granulosus* stages; structural and functional roles of non-coding genome regions; molecular 'cross-talk' between oncosphere and the immune system; and defining the precise function(s) of EG95. Applied aspects should include developing improved tools for the diagnosis and chemotherapy of cystic echinococcosis of humans.

Hydatid Cyst of the Spine: A Rare Case Report

Alkan Çeviker, S., Yüksel, C., Şener, A., Önder, T., Metineren, M., Özel, Ç., Akgül, Ö.

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Türkiye Parazitol Derg

<https://doi.org/10.4274/tpd.galenos.2021.29392>

Hydatid cyst is a zoonotic disease that can affect multiple organs and is difficult to diagnose and treat. Spinal hydatid cyst (SHC) is a rare hydatid cyst involvement observed in 1% of all cases. It can induce various neurological symptoms depending on the region of the involvement. Paraplegia is one of the most prevalent neurological symptoms. In this case report, a 63-year-old male patient with bilateral lower extremity paraplegia was operated on by neurosurgery and diagnosed with SHC at the level of Th 11 vertebra in the pathological examination of surgically removed materials. Thus, we aimed to emphasize the significance of pathological and microbiological examination in the differential diagnosis of spinal disorders.

Diagnostic tools for the detection of taeniid eggs in different environmental matrices: A systematic review.

Saelens, G., Robertson, L., Gabriël, S.

05-02-2022

Food Waterborne Parasitol

<https://doi.org/10.1016/j.fawpar.2022.e00145>

The cestode family Taeniidae consists of the genera *Echinococcus* and *Taenia*, both of which include zoonotic tapeworms of serious public health importance. Various environmental matrices have been identified from which parasite transmission to animals and humans can occur, and many techniques for detecting taeniid eggs in different environments have been developed. However, the majority lack appropriate validation, and standardized egg isolation procedures are absent. This hampers interstudy comparisons and poses a challenge for future researchers when deciding which technique to implement for assessing taeniid egg contamination in a particular matrix. Therefore, the aim of this systematic review was to present an overview of the detection methods for taeniid eggs in the environment, to discuss and compare them, and to provide recommendations for future studies. In total, 1814 publications were retrieved from scientific databases, and, ultimately, data were systematically reviewed from 90 papers. The results provide an overview of numerous diagnostic tests for taeniid egg detection in (or on) water, food, soil, insects, objects, and air. These tools could be categorized as either conventional (light microscopy), molecular, or immunodetection tools. The relatively cheap microscopy techniques often lack sensitivity and are unable to identify a taeniid egg at the genus level. Nevertheless, several records ascribed a genus, or even species, to taeniid eggs that had been detected by light microscopy. Molecular and immunodetection tools offer better specificity, but still rely on the preceding egg recovery steps that also affect overall sensitivity. Finally, the majority of the methods lacked any attempt at performance evaluation and standardization, especially at the earlier stages of the analysis (e.g., sampling strategy, storage conditions, egg recovery), and viability was rarely addressed. As such, our review highlights the need for standardized, validated detection tools, that not only assess the extent of environmental contamination, but also the egg genus or species, and address viability.

Genetic structure and phylogeography of *Echinococcus granulosus sensu stricto* genotypes G1 and G3 in Pakistan and other regions of the world based on nad5 gene.

Mehmood, N., Muqaddas, H., Ullah, M., Saarma, U., Varcasia, A.

29-01-2022

Infect Genet Evol

<https://pubmed.ncbi.nlm.nih.gov/35092843>

Pakistan is a neglected endemic focus for *Echinococcus granulosus sensu lato*, a zoonotic parasite species complex with the ability to infect wide spectrum of hosts. Wide gaps exist in literature for etiological agents of cystic echinococcosis (CE) in Pakistan due to a very low number of studies on identifying the exact genotypes involved in epidemiological manifestation of

this disease. Focusing on transmission patterns and epidemiological dynamics, this study aimed at investigating infective genotypes among the cattle population of south Punjab, Pakistan, employing a mitochondrial marker nad5 (680 bp). Nucleotide sequences retrieved from 28 hydatid cyst isolates displayed considerable intraspecific variation revealing the existence of G3 and G1 strains of *Echinococcus granulosus sensu stricto*. The G3 genotype emerged as the predominant cause (78.57%) of hydatidosis in cattle. Apart from this, to understand phylogeographical relations, homologous nucleotide sequences of the partial nad5 gene from six major regions of the world were employed in the population genetics analysis to have an insight into genetic variability and demographics of G3 genotype in particular. Diversification of G3 and its haplotypes in Pakistan (n = 11) and other regions of the world (India, Iran, Turkey, Italy and France) was demonstrated. It was further demonstrated that the South Asian population (Pakistan and India) was highly differentiated from the other regions. It could, therefore, be speculated that G3 is diverging and expanding its population with South Asia as the main focal point.

Incidental Left Ventricular Myocardial Hydatid Cyst - A case report.

Foladi, N., Farzam, F., Shah Hoshang, M., Rastin, M., Aien, M.

15-12-2021

Radiol Case Rep

<https://doi.org/10.1016/j.radcr.2021.11.040>

Hydatid disease is an indolent parasitic infection by a microorganism, echinococcosis granulosis. The disease can infect almost any human organ but is exceedingly rare involving the mediastinum and the heart. It can be lethal if complications occur. CT scan is the modality of choice for the diagnosis of the disease. The coverage of cardiac structures in the abdominal CT scan survey may be helpful for the detection of possible cardio-mediastinal hydatid disease. The authors present a case of hydatid cyst in the left ventricular wall alongside hepatic hydatid cysts. The definitive treatment includes surgery under cardiopulmonary bypass and needs to be treated as soon as it is diagnosed to prevent lethal complications.

Ultrasound-based evaluation of the prevalence of abdominal cystic echinococcosis in the Turkestan region of Kazakhstan.

Mustapayeva, A., Luca D'Alessandro, G., Doszhanova, G., Colpani, A., Sadybekov, N., Baimakhanov, Z., Assanov, E., Salybekov, S., Kaniyev, S., Serikuly, E., Tagabayeva, L., Budke, C., Vola, A., Mariconti, M., De Silvestri, A., Yalishva, S., Sadykova, A., Zholdybay, Z., Katarbayev, A., Zhakenova, Z., Brunetti, E., Juszkiwicz, K., Duisenova, A., Manciuilli, T.

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Trans R Soc Trop Med Hyg

<https://doi.org/10.1093/trstmh/trab105>

Human cystic echinococcosis (CE) is a zoonotic disease caused by *Echinococcus granulosus sensu lato*. CE is known to be endemic in some parts of Central Asia. We present findings from an ultrasound-based survey to estimate the prevalence of CE in the Turkestan oblast of Kazakhstan. In October 2019, six villages were chosen based on records from a national surveillance dataset. Inhabitants aged 5-90 y were invited to undergo a free abdominal ultrasound to screen for CE cysts. All identified cysts were staged according to the WHO-endorsed classification for CE cysts. A total of 2252 individuals underwent ultrasound screening. Twenty-two (0.98%) individuals had CE, with a combined total of 33 cysts: 25 (75.7%) inactive (14 CE4, 11 CE5) and 8 (24.3%) active/transitional (2 CE1, 1 CE2, 3 CE3a, 2 CE3b). One patient had a postsurgical cavity. Sixty-eight patients (3.0%) reported CE prior to surgical treatment. In 25 (36.8%) previously diagnosed patients, albendazole prophylaxis was not used. CE is endemic in the study region, with ongoing transmission. The number of surgically treated CE patients suggests an underestimation of the disease burden by the current surveillance system. Further studies on local CE epidemiology and the implementation of expert treatment recommendations are needed.

TREMATODOSES D'ORIGINE ALIMENTAIRE (CLONORCHIOSE, OPISTHORCHIOSE, FASCIOLASE ET PARAGONIMOSE)

Inhibition of *Schistosoma mansoni* carbonic anhydrase by the antiparasitic drug clorsulon: X-ray crystallographic and in vitro studies.

Ferraroni, M., Angeli, A., Carradori, S., Supuran, C.
18-02-2022

Acta Crystallogr D Struct Biol

<https://doi.org/10.1107/S2059798322000079>

Clorsulon is an anthelmintic drug that is clinically used against *Fasciola hepatica*. Due to the presence of two sulfonamide moieties in its core nucleus, which are well recognized as zinc-binding groups, it was proposed that it may be efficacious in the inhibition of parasite carbonic anhydrases (CAs). Proteomic analyses revealed the presence of CA in the tegument of *Schistosoma mansoni*, and recently the druggability of this target was explored by testing the inhibitory activities of several sulfonamide-based derivatives. According to the principles of drug repurposing, the aim was to demonstrate a putative new mechanism of action of clorsulon and thus widen its antiparasitic spectrum. For this purpose, the inhibitory activity and isoform selectivity of clorsulon was studied using human CA I and *S. mansoni* CA, revealing different modes of binding of clorsulon that explain its inhibitory potency against the two

enzymes. The information obtained in this study could be crucial in the design of more active and selective derivatives.

Liver fluke in beef cattle - Impact on production efficiency and associated greenhouse gas emissions estimated using causal inference methods.

Jonsson, N., MacLeod, M., Hayward, A., McNeilly, T., Ferguson, K., Skuce, P.

07-01-2022

Prev Vet Med

<https://pubmed.ncbi.nlm.nih.gov/35066320>

We aimed to estimate 1) the marginal effect of liver fluke (*Fasciola hepatica*) infection on productivity of Scottish beef cattle, and 2) the associated greenhouse gas emissions intensity (GHG EI). Data comprised 240,065 abattoir records from NE Scotland from 2014 to 2017, including the presence or absence of lesions typical of liver fluke in the liver at the time of slaughter, from which we inferred liver fluke infection status. The retrospective analysis of abattoir records to estimate marginal effects of an exposure is complicated by the multi-dimensional, clustered nature of the datasets, which result in confounding of potential causal factors with the exposure. Causal inference methods are required to identify and correct for variation in background exposure. We constructed directed acyclic graphs (DAGs) of observed variables, including the potential confounders, breed, sex, breeder, finisher, season of birth and year of birth. We then applied inverse probability weighting (IPW) to adjust for variation among exposure risk and applied a doubly robust generalized linear model (DRGLM) to the weighted observations to estimate the marginal effect of fluke on the growth rate of animals and total days from birth until slaughter. We compared these estimates with the results of linear mixed effects (LME) models with the same variables, treating breeder and producer as random effects. To estimate GHG EI, we applied IPCC tier-2 type GHG calculations to the marginal effects estimated from IPW with DRGLM. The IPW with DRGLM model estimated that animals with active fluke lesions (adult fluke seen on postmortem inspection) gained 17 (95 % CI 12-22) g/d less saleable beef than animals with no lesions and no visible fluke. Animals with active fluke lesions were 11 (95 % CI 6.5-15) d older at slaughter weight than animals with no lesions. Animals with historic lesions in which there was scarring of the liver but in which no adult fluke were seen showed a wide variation in effect estimates, consistent with some misclassification. The effect estimates from LME models suggested slightly lower effects of fluke on growth rate and days to slaughter but with overlapping 95 % confidence intervals. Calculation of the associated GHG emissions suggest the EI of meat from a herd with no fluke is approximately 1.5 % lower than the same herd with fluke. Sustainably controlling liver fluke would have additional production benefits not included in this estimate and could therefore have a much greater impact on GHG EI in practice than demonstrated here.

A machine learning approach for modelling the occurrence of *Galba truncatula* as the major

intermediate host for *Fasciola hepatica* in Switzerland.

Roessler, A., Oehm, A., Knubben-Schweizer, G., Groll, A.
05-01-2022

Prev Vet Med

<https://pubmed.ncbi.nlm.nih.gov/35042123>

Fasciolosis caused by the trematode *Fasciola hepatica* is an important parasitosis in both livestock and humans across the globe. Chronic infections in cattle are associated with considerable economic losses. As a prerequisite for an effective control and prevention of fasciolosis in cattle fine-scale predictive models on farm-level are needed. Since disease transmission will only occur where the mollusc intermediate host is present, the objective of our research was to develop a regression model that allows to predict the local presence or absence of *Galba truncatula* as principal intermediate host for *Fasciola hepatica* in Switzerland. By implementing generalized linear mixed models (GLMMs) a total amount of 70 variables were analysed for their potential influence on the likelihood π_i of finding *Galba truncatula* at a certain site. Important site-specific features could be considered by selecting suitable modelling procedures. The statistical software R was used to conduct regression analysis, performing the *grplasso* and the *glimmLasso* method. The selection of parameters was based on 10-fold cross validation and the Bayesian Information Criterion (BIC). This yielded a total number of 19 potential predictor variables for the *grplasso* and 13 variables for the *glimmLasso* model, which also included random effects. Nine variables appeared to be relevant predictors for the occurrence of *Galba truncatula* in both models. These included reed/humid area, spring water, water bodies within a 100 m radius, and trees/bushes as powerful positive predictors. High soil depth, temperatures frequently exceeding 30 °C in the year preceding the search for snails and temperatures below 0 °C especially in the second year before were identified to exert an adverse effect on the occurrence of *Galba truncatula*. Temperatures measured near ground level proved to be more powerful predictors than macroclimatic parameters. Precipitation values seemed to be of minor impact in the given setting. Both regression models may be convenient for a fine-scale prediction of the occurrence of *Galba truncatula*, and thus provide useful approaches for the development of future spatial transmission models, mapping the risk of fasciolosis in Switzerland on farm-level.

The *fasciola cinereum* subregion of the hippocampus is important for the acquisition of visual contextual memory.

Park, S., Lim, H., Lee, E., Yoo, S., Jung, H., Lee, E., Sun, W., Lee, I.

06-01-2022

Prog Neurobiol

<https://pubmed.ncbi.nlm.nih.gov/34999186>

The *fasciola cinereum* (FC) is a subregion of the hippocampus that has received relatively little attention compared with other hippocampal subregions with respect to anatomical

characteristics and functional significance. Here, we show that the FC exhibits clear anatomical borders with the distalmost region of the CA1. Principal neurons in the FC resemble the granule cells in the dentate gyrus (DG). However, adult neurogenesis was not found unlike in the DG. The FC receives inputs mostly from the lateral entorhinal cortex and perirhinal cortex while projecting exclusively to the crest of the DG within the hippocampus. Neurotoxic lesions in the FC using colchicine impaired the acquisition, but not retrieval, of visual contextual memory in rats. FC lesions also impaired place recognition and object-in-place memory. As the rat performed the contextual memory task on the T-maze, place cells in the FC exhibited robust place fields and were indiscriminable from those in CA1 with respect to the basic firing properties. However, place cells in the FC fired only transiently in their place fields on the maze compared with those in CA1. Our findings suggest that the episodic firing patterns of the place cells in the FC may play critical roles in learning a novel contextual environment by facilitating temporally structured contextual pattern separation in the DG of the hippocampus.

On the arrival of fasciolosis in the Americas.

Vázquez, A., Alba, A., Alda, P., Vittecoq, M., Hurtrez-Boussès, S.

21-12-2021

Trends Parasitol

<https://pubmed.ncbi.nlm.nih.gov/34952798>

Fasciola hepatica is a worldwide emerging and re-emerging parasite heavily affecting several regions in South America. Some lymnaeid snail species of American origin are among the major hosts of *F. hepatica* worldwide. Recent paleoparasitological findings detected its DNA in a 2300-year-old sample in Patagonia, countering the common hypothesis of the recent arrival of *F. hepatica* in the Americas during European colonization. Thus, the theory of an initial introduction in the 1500s can no longer be sustained. This article discusses how it was possible for *F. hepatica* to reach and spread in the Americas in relation to the availability and compatibility of hosts through natural and incidental introductions. Our study will serve to better understand the ongoing Neotropical scenario of fasciolosis.

Autophagy of hepatic stellate cell induced by *Clonorchis sinensis*.

Zheng, B., Gao, Z., Liang, L., Lu, Y., Kong, Y., Chen, W., Lin, K., Chen, W., Mai, J., Li, Y., Ma, C.

25-11-2021

Mol Biol Rep

<https://doi.org/10.1007/s11033-021-07001-9>

Clonorchis sinensis was a food-borne zoonotic parasite in the worldwide and also an important risk factor of hepatic fibrosis. Excretory/secretion products of *C. sinensis* (CsESPs) are involved in parasite-host interactions and contribute to the development of hepatic damage. The aim of the present study was to investigate whether CsESPs and CsTP (adult protein)

could induce autophagy of hepatic stellate cells (HSCs) and further activate HSCs so as to participate in the pathogenesis of hepatic fibrosis. The human hepatic stellate cell line LX-2 was stimulated by CsESPs and CsTP. CsESPs showed the effect on cell proliferation in methyl thiazolyl tetrazolium (MTT) assay while CsTP failed. Autophagosomes and autolysosomes were observed after the transmission mRFP-EGFP-LC3 plasmid into the LX-2 cells. CsESPs had more powerful to induce the accumulation of autophagosomes and autolysosomes to enhance autophagic flux compared with CsTP. Western-blotting analysis confirmed that the ratio of LC3-II/I in LX-2 cells was up-regulated after CsESPs treatment for 6 h, which further proved that CsESPs could induce autophagy in LX-2 cells. Meanwhile, q-PCR results showed that the mRNA levels of collagen I, collagen III and α -SMA decreased in LX-2 cells after treatment with autophagy inhibitor chloroquine, whereas they increased when combination with CsESPs. These results suggested that CsESPs-induced autophagy might be involved in the activation of HSCs, and consequently participate in the pathogenesis of hepatic fibrosis caused by *C. sinensis* infection.

FILARIOSE LYMPHATIQUE

Comparison of Different Sampling Methods to Catch Lymphatic Filariasis Vectors in a Sudan Savannah Area of Mali.

Coulibaly, Y., Sangare, M., Dolo, H., Doumbia, S., Coulibaly, S., Dicko, I., Diabate, A., Coulibaly, M., Soumaoro, L., Diallo, A., Dembele, M., Traore, S., Stanton, M., Koudou, B., Klion, A., Nutman, T., Kelly-Hope, L., Bockarie, M.

28-02-2022

Am J Trop Med Hyg

<https://doi.org/10.4269/ajtmh.21-0667>

There is a need for better tools to monitor the transmission of lymphatic filariasis and malaria in areas undergoing interventions to interrupt transmission. Therefore, mosquito collection methods other than human landing catch (HLC) are needed. This study aimed to compare the Ifakara tent trap type C (ITTC) and the Biogents sentinel trap (BGST) to the HLC in areas with different vector densities. Mosquitoes were collected in two villages in Mali from July to December in 2011 and 2012. The three methods were implemented at each site with one ITTC, one BGST, and one HLC unit that consisted of one room with two collectors-one indoor and the other outdoor. The Anopheles collected in 2011 were individually dissected, whereas those from 2012 were screened in pools using reverse transcription-polymerase chain reaction (RT-PCR) to determine the maximum infection prevalence likelihood (MIPL) for *Wuchereria bancrofti* and *Plasmodium falciparum*. The dissection of the females also allowed to assess the parity rates, as well its results. Over the 2 years, the HLC method collected 1,019 Anopheles, yields that were 34- and 1.5-fold higher than those with the BGST and ITTC, respectively. None

of the dissected Anopheles were infected. The RT-PCR results showed comparable MIPL between HLC and ITTC for *W. bancrofti* with one infected pool from each trap's yield (respectively 0.03% [0.0009-0.2%] and 0.04% [0.001-0.2%]). For *P. falciparum*, no infected pool was recovered from BGST. The ITTC is a good alternative to HLC for xenomonitoring of program activities.

Broadening the range of use cases for ivermectin - a review of the evidence.

Kositz, C., Bradley, J., Hutchins, H., Last, A., D'Alessandro, U., Marks, M.

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Trans R Soc Trop Med Hyg

<https://doi.org/10.1093/trstmh/trab114>

Ivermectin is a broad-spectrum antiparasitic agent that interferes with glutamate-gated chloride channels found in invertebrates but not in vertebrate species. Mass drug administration (MDA) with ivermectin-based regimes has been a mainstay of elimination efforts targeting onchocerciasis and lymphatic filariasis for more than 3 decades. More recently, interest in the use of ivermectin to control other neglected tropical diseases (NTDs) such as soil-transmitted helminths and scabies has grown. Interest has been further stimulated by the fact that ivermectin displays endectocidal efficacy against various Anopheles species capable of transmitting malaria. Therefore there is growing interest in using ivermectin MDA as a tool that might aid in the control of both malaria and several NTDs. In this review we outline the evidence base to date on these emerging indications for ivermectin MDA with reference to clinical and public health data and discuss the rationale for evaluating the range of impacts of a malaria ivermectin MDA on other NTDs.

MYCETOME

In depth search of the Sequence Read Archive database reveals global distribution of the emerging pathogenic fungus *Scedosporium aurantiacum*.

Irinyi, L., Rope, M., Meyer, W.

04-03-2022

Med Mycol

<https://pubmed.ncbi.nlm.nih.gov/35244718>

Scedosporium species are emerging opportunistic fungal pathogens causing various infections mainly in immunocompromised patients, but also in immunocompetent individuals, following traumatic injuries. Clinical manifestations range from local infections, such as subcutaneous mycetoma or bone and joint infections, to pulmonary colonization and severe disseminated diseases. They are commonly found in soil and other environmental sources. To date *S. aurantiacum* has been

reported only from a handful of countries. To identify the worldwide distribution of this species we screened publicly available sequencing data from fungal metabarcoding studies in the Sequence Read Archive (SRA) of The National Centre for Biotechnology Information (NCBI) by multiple BLAST searches. *S. aurantiacum* was found in 26 countries and two islands, throughout every climatic region. This distribution is like that of other *Scedosporium* species. Several new environmental sources of *S. aurantiacum* including human and bovine milk, chicken and canine gut, freshwater, and faeces of the giant white-tailed rat (*Uromys caudimaculatus*) were identified. This study demonstrated that raw sequence data stored in the SRA database can be repurposed using a big data analysis approach to answer biological questions of interest.

Canine eumycetoma caused by *Madurella pseudomycetomatis*.

Albanese, F., Muscatello, L., Michelutti, A., Falcaro, C., Bellentani, L., Danesi, P.

01-02-2022

Med Mycol Case Rep

<https://doi.org/10.1016/j.mmcr.2022.01.007>

Canine eumycetoma is a rare granulomatous disease caused by dematiaceous fungi. A 2-year-old Great Dane dog had a subcutaneous mass in the right thigh that was surgically removed. Grossly, numerous black-grains were visible. Histologically subcutaneous pyogranulomas were centered on myriads of pigmented fungal elements. *Madurella pseudomycetomatis* was molecularly characterized.

A combination of trimethoprim/sulfamethoxazole with linezolid is useful for actinomycetoma: A summary of the existing data and the rationale of combination therapy.

Sardana, K., Sachdeva, S.

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Indian J Dermatol Venereol Leprol

https://doi.org/10.25259/IJDVL_539_2021

ONCHOCERCOSE

Reducing onchocerciasis-associated morbidity in onchocerciasis-endemic foci with high ongoing transmission: a focus on the children.

Colebunders, R., Kaiser, C., Basáñez, M., Olliaro, P., Lakwo, T., Siewe Fodjo, J.

21-01-2022

Int J Infect Dis

<https://pubmed.ncbi.nlm.nih.gov/35074518>

Efforts are being directed toward the elimination of onchocerciasis transmission in endemic areas with community-directed treatment with ivermectin (CDTI) in Africa, which greatly reduces onchocerciasis-associated disease. However, onchocerciasis remains a major public health problem in areas of South Sudan, the Democratic Republic of the Congo, Cameroon, and the Central African Republic. Strengthening onchocerciasis elimination efforts in areas with a high prevalence of disease burden is crucial to decrease transmission, morbidity, and mortality. We argue that clinical trials are needed to investigate the safety and efficacy of ivermectin treatment of *Onchocerca volvulus*-infected pregnant women and children younger than 5 years. Crucially, 6-monthly administration of ivermectin in school-age children at risk of onchocerciasis-associated epilepsy could be achieved by supplementing annual CDTI with an extra round of ivermectin treatment during Child Health Days in schools and/or other distribution sites every year. These strategies would help achieve the elimination of onchocerciasis and its associated disease burden.

SCHISTOSOMIASE

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.

Infection history and current co-infection with *Schistosoma mansoni* decreases *Plasmodium* species intensities in pre-school children from Uganda.

McDowell, D., Hurt, L., Kabatereine, N., Stothard, J., Lello, J.

05-03-2022

J Infect Dis

<https://pubmed.ncbi.nlm.nih.gov/35245932>

Malaria-schistosomiasis co-infections are common in sub-Saharan Africa but studies present equivocal results regarding the inter-specific relationships between these parasites. Through mixed model analyses of a dataset of Ugandan preschool children, we explore how current co-infection and prior infection with either *Schistosoma mansoni* or *Plasmodium*

species, alter subsequent 1) Plasmodium intensity 2) Plasmodium risk and 3) *S. mansoni* risk. Co-infection and prior infections with *S. mansoni* were associated with reduced Plasmodium intensity, moderated by prior Plasmodium infections, wealth and host age. Future work should assess whether these interactions impact host health and parasite control efficacy in this vulnerable age group.

Traditional Kenyan herbal medicine: exploring natural products' therapeutics against schistosomiasis.

Ndegwa, F., Kondam, C., Aboagye, S., Esan, T., Waxali, Z., Miller, M., Gikonyo, N., Mbugua, P., Okemo, P., Williams, D., Hagen, T.

03-03-2022

J Helminthol

<https://doi.org/10.1017/S0022149X22000074>

Praziquantel (PZQ) remains the only drug of choice for the treatment of schistosomiasis, caused by parasitic flatworms. The widespread use of PZQ in schistosomiasis endemic areas for about four decades raises concerns about the emergence of resistance of *Schistosoma* spp. to PZQ under drug selection pressure. This reinforces the urgency in finding alternative therapeutic options that could replace or complement PZQ. We explored the potential of medicinal plants commonly used by indigenes in Kenya for the treatment of various ailments including malaria, pneumonia, and diarrhoea for their antischistosomal properties. Employing the Soxhlet extraction method with different solvents, seven medicinal plants *Artemisia annua*, *Ajuga remota*, *Bredilia micrantha*, *Cordia africana*, *Physalis peruviana*, *Prunus africana* and *Senna didymobotrya* were extracted. Qualitative phytochemical screening was performed to determine the presence of various phytochemicals in the plant extracts. Extracts were tested against *Schistosoma mansoni* newly transformed schistosomula (NTS) and adult worms and the schistosomicidal activity was determined by using the adenosine triphosphate quantitation assay. Phytochemical analysis of the extracts showed different classes of compounds such as alkaloids, tannins, terpenes, etc., in plant extracts active against *S. mansoni* worms. Seven extracts out of 22 resulted in <20% viability against NTS in 24 h at 100 µg/ml. Five of the extracts with inhibitory activity against NTS showed >69.7% and ≥72.4% reduction in viability against adult worms after exposure for 24 and 48 h, respectively. This study provides encouraging preliminary evidence that extracts of Kenyan medicinal plants deserve further study as potential alternative therapeutics that may form the basis for the development of the new treatments for schistosomiasis.

Novel Hepatic Schistosomula Antigens as Promising Targets for Immunodiagnosis and Immunoprotection of Schistosomiasis japonica.

Hou, N., Piao, X., Jiang, N., Liu, S., Cai, P., Liu, B., McManus, D., Chen, Q.

02-03-2022

J Infect Dis

<https://pubmed.ncbi.nlm.nih.gov/35235942>

Antigens of migrating schistosomula are promising candidates as schistosomiasis vaccine targets, since immune attack on hepatic schistosomula would interrupt the parasites life cycle and reduce egg burden on the host. Here, we report a collection of *Schistosoma japonicum* schistosomula proteins (SjScP), which are highly expressed in hepatic schistosomula. We found that a number of these SjScPs were highly antigenic and could effectively stimulate humoral immune responses in both human and other mammalian hosts. In particular, SjScP25, SjScP37, SjScP41, SjScP80, SjScP88 showed high potential as biomarkers for schistosomiasis immunodiagnosis. Furthermore, we demonstrated that immunization with several of the recombinant SjScPs were able to protect mice from *S. japonicum* challenge infection, with SjScP25 generating the most protective results. Our work represents a group of novel schistosome immunogens, which may be promising schistosomiasis japonica diagnosis and vaccine candidates.

G-quadruplexes in helminth parasites.

Cantara, A., Luo, Y., Dobrovolná, M., Bohalova, N., Fojta, M., Verga, D., Guittat, L., Cucchiari, A., Savrimoutou, S., Häberli, C., Guillon, J., Keiser, J., Brázda, V., Mergny, J.

02-03-2022

Nucleic Acids Res

<https://pubmed.ncbi.nlm.nih.gov/35234933>

Parasitic helminths infecting humans are highly prevalent infecting ~2 billion people worldwide, causing inflammatory responses, malnutrition and anemia that are the primary cause of morbidity. In addition, helminth infections of cattle have a significant economic impact on livestock production, milk yield and fertility. The etiological agents of helminth infections are mainly Nematodes (roundworms) and Platyhelminths (flatworms). G-quadruplexes (G4) are unusual nucleic acid structures formed by G-rich sequences that can be recognized by specific G4 ligands. Here we used the G4Hunter Web Tool to identify and compare potential G4 sequences (PQS) in the nuclear and mitochondrial genomes of various helminths to identify G4 ligand targets. PQS are nonrandomly distributed in these genomes and often located in the proximity of genes. Unexpectedly, a Nematode, *Ascaris lumbricoides*, was found to be highly enriched in stable PQS. This species can tolerate high-stability G4 structures, which are not counter selected at all, in stark contrast to most other species. We experimentally confirmed G4 formation for sequences found in four different parasitic helminths. Small molecules able to selectively recognize G4 were found to bind to *Schistosoma mansoni* G4 motifs. Two of these ligands demonstrated potent activity both against larval and adult stages of this parasite.

Inhibition of Schistosoma mansoni carbonic anhydrase by the antiparasitic drug clorsulon: X-ray crystallographic and in vitro studies.

Ferraroni, M., Angeli, A., Carradori, S., Supuran, C.

18-02-2022

Acta Crystallogr D Struct Biol<https://doi.org/10.1107/S2059798322000079>

Clorsulon is an anthelmintic drug that is clinically used against *Fasciola hepatica*. Due to the presence of two sulfonamide moieties in its core nucleus, which are well recognized as zinc-binding groups, it was proposed that it may be efficacious in the inhibition of parasite carbonic anhydrases (CAs). Proteomic analyses revealed the presence of CA in the tegument of *Schistosoma mansoni*, and recently the druggability of this target was explored by testing the inhibitory activities of several sulfonamide-based derivatives. According to the principles of drug repurposing, the aim was to demonstrate a putative new mechanism of action of clorsulon and thus widen its antiparasitic spectrum. For this purpose, the inhibitory activity and isoform selectivity of clorsulon was studied using human CA I and *S. mansoni* CA, revealing different modes of binding of clorsulon that explain its inhibitory potency against the two enzymes. The information obtained in this study could be crucial in the design of more active and selective derivatives.

In vivo and in vitro anti-schistosomiasis effect of garlic (*Allium sativum*): a systematic review.

Shakib, P., Kalani, H., Ali, A., Zebardastpour, M., Moradpour, K., Ho, J., Nazarabad, V., Cheraghpour, K.

28-02-2022

Curr Drug Discov Technol<https://doi.org/10.2174/1570163819666220228154752>

Garlic (*Allium sativum*) is currently used as a natural supplement for the treatment of various diseases and disorders, because it has antibacterial, antiviral, antifungal, antiparasitic, antioxidant, and anti-inflammatory properties. This systematic review aimed to summarize the in vitro and in vivo effects of garlic against *Schistosoma* spp. The current study was carried out according to the PRISMA guideline and registered in the CAMARADES-NC3Rs Preclinical Systematic Review and Meta-analysis Facility (SyRF) database. Literature search was conducted using five databases; namely Scopus, PubMed, Web of Science, EMBASE, and Google Scholar from January 2008 to January 2021. The search was restricted to articles published in English language. The search was performed using appropriate syntax and specific tags for each database. Of 2,600 studies, 10 met the eligibility criteria for review. All studies used *Schistosoma mansoni* and garlic. Ten studies (90%) were performed in vivo and one study in vitro. The results of studies showed that garlic can remove the parasite through a direct effect on the parasite itself, such as changes in the parasite's coat or destruction of its spines, or indirectly by strengthening the immune response against the parasite. Effective anti-schistosomal responses of garlic in studies show that the active compounds of garlic can be used as a complement with chemical drugs or as an alternative for them, and this is needed to optimize the consumption of these active compounds for medicinal uses.

Sensitive Diagnosis and Post-Treatment Follow-Up of *Schistosoma mansoni* Infections in Asymptomatic Eritrean Refugees by Circulating Anodic Antigen Detection and Polymerase Chain Reaction.

Hoekstra, P., Chernet, A., de Dood, C., Brienen, E., Corstjens, P., Labhardt, N., Nickel, B., Wammes, L., van Dam, G., Neumayr, A., van Lieshout, L.

28-02-2022

Am J Trop Med Hyg<https://doi.org/10.4269/ajtmh.21-0803>

The increasing number of refugees coming from or passing through *Schistosoma*-endemic areas and arriving in Europe highlights the importance of screening for schistosomiasis on arrival, and focuses attention on the choice of diagnostic test. We evaluate the diagnostic performance of circulating anodic antigen (CAA) detection in 92 asymptomatic refugees from Eritrea. Results were compared with already-available stool microscopy, serology, and urine point-of-care circulating cathodic antigen (POC-CCA) data. For a full diagnostic comparison, real-time polymerase chain reaction (PCR) and the POC-CCA were included. All outcomes were compared against a composite reference standard. Urine and serum samples were subjected to the ultra-sensitive and highly specific up-converting particle lateral flow CAA test, *Schistosoma* spp. real-time PCR was performed on urine and stool, and the POC-CCA was used on urine using the G-score method. CAA was detected in 43% of urine and in 40% of serum samples. Urine PCR was negative in all 92 individuals, whereas 25% showed *Schistosoma* DNA in stool. POC-CCA was positive in 30% of individuals. The CAA test confirmed all microscopy positives, except for two cases that were also negative by all other diagnostic procedures. Post-treatment, a significant reduction in the number of positives and infection intensity was observed, in particular regarding CAA levels. Our findings confirm that microscopy, serology, and POC-CCA lack the sensitivity to detect all active *Schistosoma* infections. Accuracy of stool PCR was similar to microscopy, indicating that this method also lacks sensitivity. The CAA test appeared to be the most accurate method for screening active *Schistosoma* infections and for monitoring treatment efficacy.

Potentiality of curcumin on ISHAK scoring system and the expressions of BAX, IL-17A, and EGF in the treatment of *Schistosoma mansoni* infection using Swiss albino mice.

El Saftawy, E., El-Dardiry, M., Abd-Elal, A., Negm, M., Amin, N.

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Trop Biomed<https://doi.org/10.47665/tb.39.1.001>

The present study evaluated the antiparasitic effect of curcumin extract on *Schistosoma mansoni* in Swiss albino mice. The experimental design included four groups of *S. mansoni* - infected mice; without treatment (controls), curcumin-treated, Praziquantel (PZQ)-treated, and PZQ + curcumin treated mice. The results showed that curcumin improved ISHAK confluent

necrosis score up to zero. PZQ +curcumin showed a significant reduction in portal inflammation. Both activity and fibrosis demonstrated lower scores in all treated groups, however, PZQ revealed a marked increase in confluent necrosis and interface hepatitis. Besides, the lobular inflammation revealed worsening in the overall ISHAK score in all treated groups compared with the control. Few periocular granulomas were recovered by PZQ +curcumin treatment at day 35 post-treatment (6 ± 1.2), P-value < 0.05 . Curcumin revealed a mild reduction (60 ± 7.376). Curcumin-treated groups, with and without PZQ, resulted in higher significant Immunoreactivity score (IRS) for Bcl-2-associated X (BAX) and lower Interleukine-17A (IL-17A), and Human epidermal growth factor (EGF), compared to the control. However, PZQ revealed a lower mean IRS value in BAX, higher IL-17A and EGF in the periovulatory granuloma. It was concluded that PZQ +curcumin treatment had a potent synergistic outcome through lessening the number of granulomas, the inflammatory events, and the expression of EGF, and amelioration of apoptosis in the periovulatory granulomas if compared with either PZQ or curcumin alone.

Larval trematodes hosted by *Biomphalaria straminea* in the Brazilian semiarid region: implications for schistosomiasis control.

Sousa, D., Carvalho-Costa, F., Monteiro, K., Silva, E., Castro, E., Sousa, R., Moraes Neto, A.

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Trop Biomed

<https://doi.org/10.47665/tb.39.1.003>

The present study aimed to identify larval trematodes shed by snails found in water bodies used by urban communities in a former schistosomiasis endemic area in the state of Piauí, in the Brazilian semiarid region. A malacological survey was performed followed by analysis of the cercariae shed by the snails after light exposure. *Biomphalaria straminea* specimens ($n=1,224$) were obtained from all seven collection sites. Cercariae shed by snails were i) single tailed, in which one type of cercariae was identified (*Echinostoma* cercariae), and ii) with bifurcated tail (brevifurcate apharyngeate distome, brevifurcate pharyngeate distome, and longifurcate pharyngeate distome [strigeocercaria]). Brevifurcate apharyngeate distome were further examined and the presence of spikes in swimming membranes enabled the identification of Spirorchiiidae cercariae in all individuals, demonstrating the absence of cercariae compatible with *Schistosoma mansoni*. Nevertheless, the accurate diagnosis of *S. mansoni* circulation in former endemic areas is still necessary.

Neuroretinitis with secondary retinal venous stasis in a patient with Schistosomiasis.

Pizem, H., Ben-Arie-Weintrob, Y., Naaman, E.

29-01-2022

Am J Ophthalmol Case Rep

<https://doi.org/10.1016/j.ajoc.2022.101355>

Schistosomiasis, one of the most important parasitic diseases in humans, is caused by the trematode parasites. Common manifestations include gastrointestinal and genitourinary symptoms while ophthalmologic involvement is rare. Here we report a case of retinal vein occlusion and neuroretinitis secondary to a schistosomiasis infection. A healthy 23-year-old man presented with headache and decreased vision in his right eye. Ophthalmic examination revealed a swollen disc, engorged retinal veins with retinal hemorrhages in all quadrants and macular edema with hard exudates ('macular star'). Fluorescein Angiography demonstrated a hot disk and an irregular pattern of filling defects along a major retinal vein. Further questioning revealed that a few months earlier, the patient had returned from an endemic area and was found seropositive for schistosomiasis. In this case of neuroretinitis and secondary retinal venous stasis, the presumed underlying mechanism is associated with embolization of *Schistosoma* eggs or deposition of immune complexes. Although ophthalmic manifestations of schistosomiasis are rare, awareness should be maintained especially among world-travelers with unusual ocular findings.

Profile of T and B lymphocytes in individuals resistant to *Schistosoma mansoni* infection.

da Paixão de Souza, R., Araújo, M., Lopes, D., Oliveira, S., Fernandes, J., de Jesus, K., Carvalho, E., Oliveira, R., Cardoso, L.

08-02-2022

Parasitol Res

<https://doi.org/10.1007/s00436-022-07435-5>

The mechanisms involved in the development of resistance to infection/reinfection by *Schistosoma mansoni* still arouse great interest and controversy. Some authors demonstrate that resistance to infection is attributed to a mixed Th1 and Th2 response and resistance to reinfection after repeated treatments through mechanisms associated with the Th2 response. Through flow cytometry, the phenotypic characterization of B and T lymphocytes in individuals residing in endemic areas with low parasite loads over 10 years was evaluated for the first time in humans. In this study, individuals with low parasite loads for *Schistosoma mansoni* had a higher proportion of Th1 and Th2 cells. In addition, lymphocytes from these individuals showed a higher degree of expression of costimulatory molecules CD28 and CTLA-4 and regulatory molecules FoxP3 and IL-10, when compared to individuals with high parasite loads. Our data indicate that the control of the parasite load of *S. mansoni* must be associated with a Th1, Th2, and regulatory response, and that further studies are needed to elucidate the possibility of mechanisms associated with the hyporesponsiveness of lymphocytes from individuals with high parasite loads.

Antischistosomal tetrahydro- γ -carboline sulfonamides.

Ren, R., Wang, X., Leas, D., Häberli, C., Cal, M., Dong, Y., Kaiser, M., Keiser, J., Vennerstrom, J.
12-01-2022
Bioorg Med Chem Lett
<https://pubmed.ncbi.nlm.nih.gov/35031451>

We discovered tetrahydro- γ -carboline sulfonamides as a new antischistosomal chemotype. The aryl sulfonamide and tetrahydro- γ -carboline substructures were required for high antischistosomal activity. Increasing polarity improved solubility and metabolic stability but decreased antischistosomal activity. We identified two compounds with IC_{50} values $<5 \mu M$ against ex vivo *Schistosoma mansoni*.

Schistosome TRPML channels play a role in neuromuscular activity and tegumental integrity.

Bais, S., Norwillo, A., Ruthel, G., Herbert, D., Freedman, B., Greenberg, R.
03-01-2022
Biochimie
<https://pubmed.ncbi.nlm.nih.gov/34990770>

Schistosomiasis is a neglected tropical disease caused by parasitic flatworms of the genus *Schistosoma*. Monotherapeutic treatment of this disease with the drug praziquantel, presents challenges such as inactivity against immature worms and inability to prevent reinfection. Importantly, ion channels are important targets for many current anthelmintics. Transient receptor potential (TRP) channels are important mediators of sensory signals with marked effects on cellular functions and signaling pathways. TRPML channels are a class of Ca^{2+} -permeable TRP channels expressed on endolysosomal membranes. They regulate lysosomal function and trafficking, among other functions. *Schistosoma mansoni* is predicted to have a single TRPML gene (SmTRPML) with two splice variants differing by 12 amino acids. This study focuses on exploring the physiological properties of SmTRPML channels to better understand their role in schistosomes. In mammalian cells expressing SmTRPML, TRPML activators elicit a rise in intracellular Ca^{2+} . In these cells, SmTRPML localizes both to lysosomes and the plasma membrane. These same TRPML activators elicit an increase in adult worm motility that is dependent on SmTRPML expression, indicating a role for these channels in parasite neuromuscular activity. Suppression of SmTRPML in adult worms, or exposure of adult worms to TRPML inhibitors, results in tegumental vacuolations, balloon-like surface exudates, and membrane blebbing, similar to that found following TRPML loss in other organisms. Together, these findings indicate that SmTRPML may regulate the function of the schistosome endolysosomal system. Further, the role of SmTRPML in neuromuscular activity and in parasite tegumental integrity establishes this channel as a candidate anti-schistosome drug target.

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

G-quadruplexes in helminth parasites.

Cantara, A., Luo, Y., Dobrovolná, M., Bohalova, N., Fojta, M., Verga, D., Guittat, L., Cucchiari, A., Savrimoutou, S., Häberli, C., Guillon, J., Keiser, J., Brázda, V., Mergny, J.
02-03-2022
Nucleic Acids Res
<https://pubmed.ncbi.nlm.nih.gov/35234933>

Parasitic helminths infecting humans are highly prevalent infecting ~2 billion people worldwide, causing inflammatory responses, malnutrition and anemia that are the primary cause of morbidity. In addition, helminth infections of cattle have a significant economic impact on livestock production, milk yield and fertility. The etiological agents of helminth infections are mainly Nematodes (roundworms) and Platyhelminths (flatworms). G-quadruplexes (G4) are unusual nucleic acid structures formed by G-rich sequences that can be recognized by specific G4 ligands. Here we used the G4Hunter Web Tool to identify and compare potential G4 sequences (PQS) in the nuclear and mitochondrial genomes of various helminths to identify G4 ligand targets. PQS are nonrandomly distributed in these genomes and often located in the proximity of genes. Unexpectedly, a Nematode, *Ascaris lumbricoides*, was found to be highly enriched in stable PQS. This species can tolerate high-stability G4 structures, which are not counter selected at all, in stark contrast to most other species. We experimentally confirmed G4 formation for sequences found in four different parasitic helminths. Small molecules able to selectively recognize G4 were found to bind to *Schistosoma mansoni* G4 motifs. Two of these ligands demonstrated potent activity both against larval and adult stages of this parasite.

Mid-7th century BC human parasite remains from Jerusalem.

Langgut, D.
12-11-2021
Int J Paleopathol
<https://pubmed.ncbi.nlm.nih.gov/34781239>

To determine the species of intestinal parasites present in 7th century BC high-status residents of Jerusalem and to expose the history of regional health and sanitary conditions. Fifteen sediment samples were collected from the cesspit below a stone toilet seat found at the site of Armon Hanatziv, southern Jerusalem. The toilet installation was located in a garden adjacent to a monumental structure with extraordinary architectural elements. A light microscope was used to identify and measure the eggs. The presence of four intestinal parasite egg taxa was detected: *Trichuris trichiura* (whipworm), *Taenia* sp. (beef/pork tapeworm), *Ascaris lumbricoides* (roundworm), and *Enterobius vermicularis* (pinworm). This is the earliest appearance of roundworm and pinworm in the ancient Israel

parasitological record. Findings reveal that intestinal parasitic diseases most likely caused by poor sanitary conditions were a human problem in the Late Iron Age of Israel, affecting even high-status groups. The study demonstrates the potential of archaeoparasitological investigations to expand our knowledge of the origin and history of regional infections. Moreover, parasitological evidence enabled us to determine the purpose of the cubical perforated stone artifacts (stone toilet seats rather than cultic objects as currently debated). The eggs of some parasite taxa are less durable, so may theoretically be absent due to selective preservation. Future excavations of ancient Israel should include archaeoparasitological studies of rare toilet installations to prevent information loss of regional history of diseases and to better understand their archaeological context.

GALE

Health and illness in migrants and refugees arriving in Europe: analysis of the electronic personal health record system.

Zenner, D., Méndez, A., Schillinger, S., Val, E., Wickramage, K.

02-03-2022

J Travel Med

<https://pubmed.ncbi.nlm.nih.gov/35238944>

The electronic Personal Health(ePHR) Record is a health information system that registers health data on newly arriving migrants and was implemented in eight European countries (Bulgaria, Croatia, Cyprus, Greece, Italy, Romania, Serbia, and Slovenia). This is a cross-sectional study aimed to describe the health problems and health status of all migrants attended at health clinics as part of the health assessment programme established in the reception centres(2016-2019). Data were collected on demographics, clinical and laboratory findings and diagnostics performed, including medical records. We classified all diseases using pre-specified algorithms according to information on prespecified variables from the ePHR questionnaire, ICD-10 codes, positive laboratory findings or review of medical records. Crude proportions were calculated and odds ratios estimated using logistic regression modelling. The ePHR dataset contained a total of 19564 clinical episodes in 14436 individuals, recorded between January 2016 to October 2019. Most individuals (75%) were refugees or asylum seekers (22%) from 92 different nationalities. There were 2531/19564(12,9%) infectious diseases episodes reported during the study period, being 1283/2531(50.7%) of them pharyngo-tonsillitis, 529(20.9%) scabies, 158(6.2%) viral hepatitis, 156(6.1%) lower respiratory infections. There were 2462(17.1%) individuals with non-communicable diseases reported; including 821(5.7%) cardiovascular diseases, 1183(8.2%) neurological condition, 644(4.5%) Diabetes mellitus and 212(1.5%) kidney disease cases. Having Diabetes

Mellitus (adjusted OR 3.3,[95%CI 2.7-4.1], $p<0.001$), and neurological disorders (aOR 1.8,[95%CI 1.4-2.2], $p<0.001$) were associated with cardiovascular disorders in the multivariable logistic regression model. Mental health problems were reported in 641/14436(4.4%) individuals and were associated with increasing age. Furthermore, 610 episodes of acute injuries were reported among 585/14436(4.1%) people, 517(88.4%) of them in men, ($p<0.001$). The ePHR is a valuable tool to efficiently collect health-related data to better address migrant health issues. We described a mostly healthy population with many acute infectious disease episodes particularly in children, but also with significant number of chronic conditions and less frequent injuries or mental health problems.

Scabies Surreptitious (Bullous Scabies) Presenting as Bullous Impetigo in a Child.

Khan, R., Muzammil, A., Siddiqi, S., Qasim, S., Nadeem, A.

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J Coll Physicians Surg Pak

<https://doi.org/10.29271/jcpsp.2022.03.380>

Bullous scabies (BS) is a rare and atypical presentation of scabies, usually affecting elderly males during the seventh decade of life. BS is characterised by intense pruritic eruptions, nocturnal itch, and characteristic blisters with or without burrows in scabies-prone areas. The scabies lesions might predispose patients to bacterial super-infections, resulting in bullae formation similar to bullous impetigo. The diagnosis of BS is often puzzling and delayed. Few cases of BS have been reported among children globally. We, herein, report a case of BS in an eight-year boy from Pakistan, treated successfully with 5% topical permethrin and 2% mupirocin. Complete healing was noted within four weeks with no recurrence at two months follow-up. Key Words: Scabies, Bullous, Child, Diagnosis, Treatment.

Drug dose and animal welfare: important considerations in the treatment of wildlife.

Mounsey, K., Harvey, R., Wilkinson, V., Takano, K., Old, J., Stannard, H., Wicker, L., Phalen, D., Carver, S.

11-02-2022

Parasitol Res

<https://doi.org/10.1007/s00436-022-07460-4>

A recent publication in Parasitology Research by (Old et al. Parasitol Res 120:1077-1090, 2021) raises the topical and often controversial issue of the treatment of wildlife by personnel with little or no formal scientific training (e.g. wildlife carers). In a valuable contribution to the subject, Old and colleagues document a wide range of topical (pour-on) application doses and frequencies of moxidectin (Cydectin®) administered in situ to bare-nosed wombats (*Vombatus ursinus*) by members of the wildlife carer/treater community in southeast Australia to treat sarcoptic mange disease. This treatment occurred under minor use permits issued by the Australian Pesticides and Veterinary Management Authority (APVMA). These permits do not require

veterinary supervision, although carers are registered and are expected to comply with the guidelines of this permit. The prevalence and severity of sarcoptic mange in wildlife is influenced by a variety of factors including mite biology, environmental conditions, population density, animal behaviour and immune susceptibility (Browne et al. *Bioscience*, 2021). In bare-nosed wombats, combinations of these elements play a substantial role in making the treatment of an already difficult disease more complex. (Moroni et al. *Parasit Vectors* 13:471, 2020) comment that any pharmacological treatment of free-ranging wildlife must consider these factors when assessing their feasibility and implications, especially in the context of emerging drug resistance and potential long-term ecological impacts. As individuals with significant interest in sarcoptic mange and representing a range of professional research and veterinary expertise, we see value in providing expert commentary on this issue.

Autobiography of a Scabies Mite.

Chakraborty, A.

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Indian J Dermatol Venereol Leprol
https://doi.org/10.25259/IJDVL_718_2021

Is there a really resistance to scabies treatment with permethrin? In vitro killing activity of permethrin on *Sarcoptes scabiei* from patients with resistant scabies.

Yürekli, A.

17-12-2021

Dermatol Ther
<https://doi.org/10.1111/dth.15260>

Recently, there have been increased scabies infestations but many patients do not respond to treatment. Clinicians are hesitant to use permethrin despite the fact that treatment failure may be due to noncompliance with the treatment rather than permethrin resistance. We aimed to investigate the permethrin resistance of mites collected from patients who have endured scabies for at least 3 months despite permethrin treatment. Parasites in patients who had scabies for at least 3 months despite permethrin treatment were collected. Only parasites that were not damaged during sampling, not fragmented and had full motion were included. Parasites were divided into four groups, each with 15 parasites. Immersion oil was dripped on the control group and 5%, 7%, and 10% permethrin was added to the study groups. The responses of the parasites to the applied agents were examined using a digital microscope. All solutions, except the control group, killed the scabies mite. The mean survival time (ST) in the 5%, 7%, and 10% permethrin groups was 360 ± 33.2 , 340 ± 31.4 , and 320 ± 30.2 min, respectively. There was no statistically significant difference in the mean ST in the permethrin groups. The mean ST in the control group was 46 ± 1.5 h. The mean ST difference between the control and permethrin-treated groups was significant ($p=0.03$). There was no resistance to

permethrin, which should maintain its place as first line treatment of scabies. Treatment noncompliance, rather than permethrin resistance, seems to be the underlying factor in the chronicity of scabies.

Concomitant SARS-CoV-2 infection and crusted scabies in a 4-month infant.

Giannattasio, A., Rosa, M., Esposito, S., Di Mita, O., Angrisani, F., Acierno, S., D'Anna, C., Barbato, F., Tipo, V., Ametrano, O.

17-12-2021

J Eur Acad Dermatol Venereol
<https://doi.org/10.1111/jdv.17850>

Crusted scabies in children in France: a series of 20 cases.

Grodner, C., Miquel, J., Hadj-Rabia, S., Mallet, S., Boralevi, F., Mazereeuw-Hautier, J., Benzebouchi, N., Dhers, M., Goujon, E., Bensaïd, P., Mahé, E.

15-11-2021

Eur J Pediatr
<https://doi.org/10.1007/s00431-021-04251-4>

To evaluate the risk factors for crusted scabies in children in France. The retrospective multicenter study, conducted in France, of children (aged <18 years) with profuse and/or crusted scabies confirmed by dermoscopy and/or microscopy. Data were obtained using a standardized questionnaire. We included 20 children. The mean age was 4.5 years, and 70% of the patients were girls. Their medical history revealed a neurological pathology (agenesis of the corpus callosum; $n=1$, 5.0%), prematurity ($n=1$, 5.0%), Down syndrome ($n=1$, 5.0%), atopic dermatitis ($n=2$, 10%), and asthma ($n=2$, 10.0%). Fifteen (75.0%) children were treated with steroids before being diagnosed with scabies: 12 (60.0%) with topical steroids, one (5.0%) with a systemic steroid, and two (10.0%) with inhaled steroids. One child (5.0%) lived in a precarious environment. The mean duration of pruritus was 3.4 months, and that of the skin lesions was 3.1 months. The most commonly affected areas for crusted scabies were the palms/hands (66.7%) and the armpits (33.3%). Thirteen children (65.0%) were hospitalized, 14 (70.0%) were treated with ivermectin and all received topical treatments; 85.7% were cured within an average of 38 days, but one child had a relapse 3 months later in the form of common scabies. Conclusion: The main risk factor for developing crusted scabies in France was the misdiagnosis and the use of corticosteroids, especially topical forms typically used in "healthy" children. Management of the children was effective and similar to that used in adults. What is Known: • Crusted scabies is an extremely contagious disease which is rarely reported in infancy, especially in healthy children. • The main risk factors include immunosuppression, physical debilitation, and intellectual disability. What is New: • The main risk factor of severe scabies in this study was delayed diagnosis associated with the use of topical or systemic corticosteroids. •

The treatment was successful in 85.7% of cases, and 65% of children needed to be hospitalized.

Broadening the range of use cases for ivermectin - a review of the evidence.

Kositz, C., Bradley, J., Hutchins, H., Last, A., D'Alessandro, U., Marks, M.

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Trans R Soc Trop Med Hyg

<https://doi.org/10.1093/trstmh/trab114>

Ivermectin is a broad-spectrum antiparasitic agent that interferes with glutamate-gated chloride channels found in invertebrates but not in vertebrate species. Mass drug administration (MDA) with ivermectin-based regimes has been a mainstay of elimination efforts targeting onchocerciasis and lymphatic filariasis for more than 3 decades. More recently, interest in the use of ivermectin to control other neglected tropical diseases (NTDs) such as soil-transmitted helminths and scabies has grown. Interest has been further stimulated by the fact that ivermectin displays endectocidal efficacy against various *Anopheles* species capable of transmitting malaria. Therefore there is growing interest in using ivermectin MDA as a tool that might aid in the control of both malaria and several NTDs. In this review we outline the evidence base to date on these emerging indications for ivermectin MDA with reference to clinical and public health data and discuss the rationale for evaluating the range of impacts of a malaria ivermectin MDA on other NTDs.

Infantile Eosinophilic Pustular Folliculitis: A Case Report.

Saylam Kurtipek, G., Zekey, E., Tuncce Akyurek, F., Demirbas, A., Harmankaya, İ.

06-05-2021

J Cosmet Dermatol

<https://doi.org/10.1111/jocd.14161>

Infantile eosinophilic pustular folliculitis (I-EPF) is a rare disease characterized by pruritic vesicles and sterile pustules on the erythematous surface of the scalp and facial localization, usually seen in the neonatal period. It is essential to show the presence of dense eosinophils in the diagnosis of pustules. Histopathological examination of the hair follicles by eosinophils infiltration is determined. Here, we reported a 5-month-old baby boy diagnosed infantile eosinophilic pustular folliculitis. A 5-month-old baby boy was consulted to our polyclinic by his family because of pustules on the scalp, face, and neck developing in two week after birth. In dermatological examination, the pustular lesions of 1-2 mm in diameter on the scalp, face, and neck on an erythematous background were determined. There was no growth in the culture taken from the pustule. In the laboratory tests of the patient; upon detection of eosinophilia in the hemogram. The eosinophil count at the patient's first admission was 1.48 K/ μ l. (0.05 0.50). Eosinophil count was 0.02 K/ μ l after treatment. It was decreased. The patient was evaluated for other pustular dermatoses. In the

differential diagnosis of the patient; causing bacterial/non-bacterial pustulosis were included. Bacterial culture was negative. Eosinophilic folliculitis defines as a group of papulopustular diseases with unknown etiology characterized histologically by eosinophilic infiltrates. First, Ofuji reported a female patient with recurrent follicular pustules and peripheral eosinophilia as a variant of folliculitis in 1965. Its etiopathogenesis is not clearly known. In the differential diagnosis of EPF includes the other pustular lesions of the newborn such as erythematotoxicum neonatarum, transient neonatal pustular dermatosis, infantile acropustulosis, scabies, dermatophytosis, and langerhans cell histiocytosis. Treatment options includes topical corticosteroids and calcineurin inhibitors, antihistamines, systemic antibacterial and anti-inflammatory agents, and dapson.

A review of ethnomedicinal uses of shea butter for dermatoses in Sub-Saharan Africa.

Ugwu-Dike, P., Nambudiri, V.

02-02-2021

Dermatol Ther

<https://doi.org/10.1111/dth.14786>

Indigenous therapies, or traditional medicines (TMs), constitute a highly accessible and continuously growing health system in many parts of the world, including Sub-Saharan Africa (SSA). Shea butter, a fat produced from the kernels of the shea tree, has historically been used as an indigenous therapy for dermatologic ailments in SSA. Characterizing traditional therapeutic applications for shea butter is important to inform the continued development of TM in SSA. We conducted a literature review aimed at identifying all available publications on the use of shea butter to treat dermatoses within SSA and evaluating patterns of use. We found 24 dermatologic uses across 30 references. The most common study design was descriptive cross-sectional analysis (46.7%), often relying on the use of in-depth interviews, focus groups, and surveys. Eight SSA countries were represented and there were disparities in availability of information across SSA with the eastern and southern regions less likely to be represented. The most frequently investigated conditions were scabies, wound healing, and umbilical cord care. Shea butter was most commonly used in combination with other ingredients to produce a medical treatment with the most frequent adjuvant being *Elaeis guineensis*, African oil palm. Broad use of TM to treat varied skin diseases throughout SSA warrants increased investigations into this field in order to further develop the capacity of TM as a source of healthcare.

MORSURES DE SERPENT

Snakebite epidemiology in humans and domestic animals across the Terai region in Nepal: a multicenter random survey.

Alcoba, G., Sharma, S., Bolon, I., Ochoa, C., Babo Martins, S., Subedi, M., Shah, B., Ghimire, A., Gignoux, E., Luquero, F., Ruiz de Castañeda, R., Ray, N., Chappuis, F.

Lancet Glob Health

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Each year, 2 million people worldwide are bitten by snakes, resulting in an estimated 81 000-138 000 deaths. WHO has added snakebite envenoming to the list of neglected tropical diseases, highlighting the need for stronger epidemiological evidence in endemic countries, such as Nepal. We conducted a cross-sectional survey in villages randomly geospatially selected from aerial images from across the Nepal's Terai lowlands region (excluding towns and cities). We collected data between Nov 30, 2018 and May 7, 2019, and analysed snakebite incidence rates and outcomes in humans and domestic animals. Among 63 454 human participants living in 13 879 households (249 villages), 166 were bitten by a snake over the previous 12 months; 48.8% were envenomed and 7.8% died. This corresponded to an annual crude incidence rate of 262 snakebites (adjusted incidence of 251.1 [95% CI 201.7-312.6]) and 20 deaths (22.4 [11.9-42.1]) per 100 000 people, extrapolating to 26 749-37 661 yearly bitten people and 2386-3225 deaths. Bitten people had a median age of 30 years (IQR 20-45) and with available data, 64% were female. Children younger than 15 years (n=6; 46%) and females (n=10; 77%) were disproportionately affected among the 13 people who died. The incidence was higher in the Eastern region, and mortality was higher in the Central region. Of 183 949 animals, owners reported 144 snakebites, with an annual incidence rate of 42-202 per 100 000 and mortality of 79-100%, varying by animal type. Spatial and seasonal incidence were similar in humans and in animals. This study provides the first epidemiological estimates of snakebite envenoming in humans and domestic animals across Nepal's Terai lowlands. It was also the first to use a community-based, transdisciplinary, and One Health design. These findings call for a strengthening of preventive measures and better access to life-saving treatments. Swiss National Science Foundation project 315130_176271 (SNAKE-BYTE).

Snakebites in Jordan: A clinical and epidemiological study.

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10-01-2022

Toxicon

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The epidemiology features and clinical symptoms associated with 121 cases of snakebite requiring admission to 24 hospitals in Jordan, during 2018-2020, are discussed. Ninety-six of them (79%) brought with them to the hospital the snake that bit them or a photograph of it. *Echis coloratus* was responsible for 68 of the bites and 6 fatalities. Sex ratio was 3.2 males: 1 female, with

an overall average age of 27 ± 14.36 years. The highest incidence of bites was reported in September. Bites were most common on hands and legs. The period of hospitalization ranged from 1 to 36 days. Irbid and Karak governorates had the highest number of snakebites, most cases being reported from agricultural areas and among farmers. Clinical symptoms associated with five species of venomous snakes are described along with illustrative case histories. Symptoms associated with *Echis coloratus* bites included local swelling and necrosis, coagulopathy and bleeding, microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury (AKI) and chronic renal failure. *Daboia palaestinae* victims exhibited ecchymoses, local swelling and necrosis, with one case of angioedema. Other symptoms included thrombocytopenia, coagulopathy, microangiopathic hemolysis and local and systemic bleeding, as well as AKI. A single case of envenoming by *Macrovipera lebetinus* developed the following symptoms; swelling, severe pain, extensive ecchymoses, neutrophil leukocytosis, normochromic normocytic anemia and aggregated platelets with thrombocytopenia. Symptoms associated with two cases of *Pseudocerastes fieldi* included swelling that spread from bitten hands, and mild abnormalities of platelet count and bleeding time. Four cases of envenoming by *Atractaspis engaddensis* exhibited severe pain, local swelling, erythema, numbness and tissue necrosis. One of them developed acute systemic symptoms. The only antivenom currently available in Jordan, is VINS "Snake venom antitoxin (Biosnake)", manufactured in India using venoms of three African snakes that do not occur in Jordan. It proved clinically ineffective against envenoming by Jordanian Viperidae, failing to correct coagulopathy and life-threatening hemorrhage, and to prevent AKI.

The potential of phenolic acids in therapy against snakebites: A review.

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31-12-2021

Toxicon

<https://pubmed.ncbi.nlm.nih.gov/34979199>

Ophidism is a serious health problem worldwide and is included in the World Health Organization's (WHO's) list of Neglected Tropical Diseases. Although snakebite envenoming requires emergency treatment, currently the only treatment recommended by WHO is serotherapy, which has some disadvantages such as low access to the rural population, low effectiveness in neutralizing local effects, and high cost. In this context, new alternatives for the treatment of snakebites are required. The use of plant-derived compounds to inhibit the effects caused by snake venoms has been the object of a number of studies in recent years. This review aims to provide an up-to-date overview of the use of phenolic acids with therapeutic application against envenomation by snakes of different species. In this sense, structural analysis *in silico* and biological activities *in vivo* and *in vitro* were reported. The acids were subdivided into derivatives of benzoic and cinnamic acids, with derivatives of cinnamic acids being the most studied.

Studies have revealed that these compounds are capable of inhibiting local and systemic effects induced by envenomation, and structural analyses indicate that the acids interact with important sites responsible for the action of toxins. Thus, it was reported that phenolic acids showed antiophidic potential, providing insights for future research to develop complementary drugs for the treatment of snakebites.

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

Bowden, M., Christie, D., Hand, K., Montgomery, A.
03-01-2022

Am Surg

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Venomous snakebites are a common clinical scenario in the Southeastern United States. CroFab® (Crotalidae Polyvalent Immune Fab (Ovine), BTG, Wales, UK) antivenom is indicated in cases involving pit vipers and is known to be expensive. The treatment protocol for snakebites is based on clinically subjective measures triggering the application, or escalation of, antivenom administration. The purpose of this study is to characterize the use of CroFab at our institution and to evaluate the impact of its use regarding cost and overall outcomes. We suspect that it is often used but potentially less often needed. We hypothesized that CroFab use was associated with increased length of stay (LOS) without an observed difference in patient outcomes. A retrospective chart review of snakebite patients at our level-1 trauma center from 2000 to 2016 was performed. Snakebite location, snake species, number of vials of CroFab administered, hospital LOS, intensive care unit (ICU) LOS, and complications were identified for each patient. Patients were divided into CroFab (C) and no CroFab (NC) groups. One hundred ninety patients with venomous snakebites were included. 53.7% of patients received CroFab. There was no difference in the complication rate of C versus NC groups, ($P = .1118$). CroFab use was associated with longer hospital LOS ($P < .0001$) and ICU LOS ($P < .0001$). CroFab use was associated with increased LOS in our patient population. There was no difference in observed outcomes between the C and NC groups. These findings imply that CroFab is potentially over-used in our patient population.

A comparison between adult and paediatric snakebites and their outcomes in North Eastern South Africa.

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24-12-2021

Toxicon

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Snakebites are common among rural communities. The aim of this study was to ascertain the differences between paediatric and adult snakebite patients regarding severity, management and outcome. This study included a total of 878 patients admitted to Ngwelezana Hospital, with a snakebite or

snakebite-related complication, from September 1, 2008 to December 31, 2014. This included 274 paediatric patients (13 years and younger) and 604 adults. There was a male predominance (56%) in the paediatric group and a female predominance (51%) amongst adults. The duration between the time of the bite and presentation to the hospital was significantly longer in children. The vast majority of children and adults presented with cytotoxic envenomation. Laboratory parameters were worse amongst children in the cytotoxic group. 53 children (19%) and 44 adults (7%) required antivenom administration. Of those who received antivenom, 25% suffered adverse reactions in the paediatric group and 20% in the adult group. 56 Children (20%) underwent one or more procedures on their affected limbs compared to 26 adults (4%). The paediatric population carries a higher risk for serious morbidity and should be treated at a facility with the necessary resources. Children require antivenom more often due to severe envenomation. Delayed presentation carries significant morbidity.

Topic use of *Annona crassiflora* Mart. contributes to wound healing due to the antioxidant and proliferative effects of fibroblasts.

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08-12-2021

Injury

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Annona crassiflora Mart. is a species native to the Cerrado biome, whose fruit is known as araticum or marolo. Plant parts are widely used in folk medicine to treat inflammation and pain associated with rheumatism, wounds, venereal diseases, snakebites, and microbial infections. Thus, we investigated a fraction rich in phenolic compounds (PCAc) obtained from the crude extract of the peel of these fruits on non-cytotoxic, anti-inflammatory, antioxidant, and collagen biosynthesis properties in the healing of wounds induced on the back of BALB/c mice. For the control group, the induced wounds were not treated and for the others, wounds were treated topically with vehicle or vehicle plus PCAc. Both fractions contained in PCAc demonstrated effective protection on fibroblasts. We highlight the effect of the ethyl acetate fraction which, in addition to the protective effect, has a proliferative activity on these cells. In addition, PCAc caused improvement in healing after 7 days of treatment and in the longest period of treatment with PCAc (7, 14, and 21 days) there was a greater contraction of the wound, accompanied by resolution of the inflammatory process, antioxidant defense, increasing collagen synthesis, and modulation of metalloproteinases. PCAc demonstrated better re-epithelialization and organization of the dermis at the end of treatment. The changes promoted by the phenolic compounds of *A. crassiflora* were important in the healing process, especially in activities related to inflammation, oxidative stress, and fibrogenesis.