



Réseau MTN Francophone

# Veille scientifique Maladies tropicales négligées

**Semaine 21**

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## DENGUE, CHIKUNGUNYA ET MALADIE A VIRUS ZIKA

### A highly sensitive strand-specific multiplex RT-qPCR assay for quantitation of Zika virus replication.

Barnard, T., Wang, A., Sagan, S.

30-05-2022

*J Virol Methods*

<https://pubmed.ncbi.nlm.nih.gov/35654259>

Reverse-transcription quantitative polymerase chain reaction (RT-qPCR) is widely used to quantify viral RNA genomes for diagnostics and research, yet conventional RT-qPCR protocols are unable to accurately distinguish between the different viral RNA species that exist during infection. Here we show that false-priming and self-priming occur during reverse transcription with several published Zika virus (ZIKV) primer sets. We developed a RT-qPCR assay using tagged primers and thermostable reverse transcriptase, which greatly reduced the occurrence of nonspecific cDNA products. Furthermore, we optimized the assay for use in multiplex qPCR which allows for simultaneous quantitative detection of positive-strand and negative-strand ZIKV RNA along with an internal control from both human and mosquito cells. Importantly, this assay is sensitive enough to study early stages of virus infection in vitro. Strikingly, using this assay, we detected ZIKV negative-strand RNA as early as 3h post-infection in mammalian cell culture, at a time point prior to the onset of positive-strand RNA synthesis. Overall, the strand-specific RT-qPCR assay developed herein is a valuable tool to quantify ZIKV RNA and to study viral replication dynamics during infection. The application of these findings has the potential to increase accuracy of RNA detection methods for a variety of viral pathogens.

### ArboAlvo: stratification method for territorial receptivity to urban arboviruses.

Siqueira, A., Praça, H., Santos, J., Albuquerque, H., Pereira, L., Simões, T., Gusmão, E., Pereira, A., Pimenta Júnior, F., Nobre, A., Alves, M., Barcellos, C., Carvalho, M., Sabroza, P., Honório, N.

27-05-2022

*Rev Saude Publica*

<https://pubmed.ncbi.nlm.nih.gov/35649086>

**Objective:** To present the urban arboviruses (dengue, zika and chikungunya) stratification methodology by the territorial receptivity Index, an instrument for the surveillance and control of these diseases, which considers the heterogeneity of an intra-municipal territory. **Methods:** Ecological study that uses as unit of analysis the areas covered by health centers in Belo Horizonte. For the development of a territorial receptivity index, indicators of socio-environmental determination of urban arboviruses were selected in order to integrate the analysis of main components. The resulting components were weighted by the analytic hierarchy process and combined via

map algebra. **Results:** The territorial receptivity index showed great heterogeneity of urban infrastructure conditions. The areas classified with high and very high receptivity correspond to approximately 33% of the occupied area and are mainly concentrated in the administrative planning regions of East, Northeast, North, West, and Barreiro, especially in areas surrounding the municipality. When the density of dengue cases and Aedes eggs, from 2016, were superimposed with the stratification by the index of territorial receptivity to urban arboviruses, areas of very high receptivity had a high density of cases and Aedes eggs - higher than that observed in other areas of the city, which corresponds to a very small percentage of the municipal territory (13.5%). **Conclusion:** The analyses indicate the need for the development of adequate surveillance and control actions for each context, overcoming the logic of homogeneous allocation throughout the territory.

### Identification of clinical candidates against West Nile Virus by activity screening in vitro and effect evaluation in vivo.

Tang, H., Liu, Y., Ren, R., Liu, Y., He, Y., Qi, Z., Peng, H., Zhao, P.

29-05-2022

*J Med Virol*

<https://doi.org/10.1002/jmv.27891>

The West Nile virus (WNV) is a member of flavivirus and known as its capability of causing encephalitis. There is currently no specific treatment for WNV infection. Repurposing of clinically approved drugs appeared promising for rapidly identifying effective, safe and readily available candidates for antiviral drugs. Here, we screened the small-molecule compounds with anti-WNV activity from 978 FDA-approved drugs. Four compounds, including cilnidipine, mycophenolate mofetil, nitazoxanide and teriflunomide, were found to efficiently abrogate WNV infection in vero cells and human neuroblastoma SH-SY5Y cells. The four compounds also exert broad spectrum antiviral activity against Zika virus, Japanese encephalitis virus, yellow fever virus, tick-borne encephalitis virus and chikungunya virus. Furthermore, nitazoxanide (a synthetic benzamide) and teriflunomide (an inhibitor of dihydroorotate dehydrogenase, DHODH) protected 20% and 40% mice from lethal WNV challenge, respectively. Both drugs, which are orally bioavailable and have been approved clinically for many years, may be promising therapeutics for WNV infection. Moreover, other two DHODH inhibitors ML390 and vidofludimus also displayed potent activity against WNV infection in vitro and in vivo. This article is protected by copyright. All rights reserved.

### Spontaneous spinal intradural hemorrhage in dengue fever: a case report.

Kaushik, R., Kumar, R., Kaushik, M., Saini, M., Kaushik, R.

30-05-2022

*J Med Case Rep*

<https://doi.org/10.1186/s13256-022-03451-2>

**Background:** Spontaneous spinal cord hemorrhage is

extremely rare in dengue fever. We report a case of spontaneous spinal intradural hemorrhage in dengue fever associated with severe thrombocytopenia. **Case presentation:** A 48-year-old Indian woman presented with fever and body aches followed by acute onset of paraplegia with bladder and bowel dysfunction and loss of sensations below the level of the umbilicus. She had severe thrombocytopenia and positive dengue serology. Magnetic resonance imaging of the spine showed compression of the spinal cord due to intradural hematoma at the D7-D8 vertebral level. The patient received symptomatic treatment for dengue fever and steroids. Emergency D7-D8 laminectomy with excision of the clot and dural repair was done after stabilizing the platelet count with multiple platelet transfusions. The constitutional symptoms responded well to the treatment. There was good improvement in sensory symptoms but negligible improvement in paraplegia with a change in muscle power from grade 0/5 to grade 1/5 in the postoperative period. The patient was discharged from the hospital in a stable condition, but paraplegia showed little improvement during follow-up of 1 year. **Conclusions:** Spontaneous spinal cord hemorrhage can present as acute paraplegia in dengue fever. Failure to recognize this complication can delay initiating appropriate treatment with permanent loss of neurologic function.

### Assessing community readiness to engage in dengue fever surveillance using unmanned aerial vehicles.

**Annan, E., Guo, J., Angulo-Molina, A., Yaacob, W., Aghamohammadi, N., Guetterman, T., Yavaşoglu, S., Bardosh, K., Dom, N., Zhao, B., Lopez-Lemus, U., Khan, L., Nguyen, U., Haque, U.**  
26-05-2022

*Travel Med Infect Dis*

<https://pubmed.ncbi.nlm.nih.gov/35644475>

Surveillance is a critical component of any dengue prevention and control program. There is an increasing effort to use drones in mosquito control surveillance. Due to the novelty of drones, data are scarce on the impact and acceptance of their use in the communities to collect health-related data. The use of drones raises concerns about the protection of human privacy. Here, we show how willingness to be trained and acceptance of drone use in tech-savvy communities can help further discussions in mosquito surveillance. We conducted a cross-sectional study in Malaysia, Mexico, and Turkey to assess knowledge of diseases caused by *Aedes* mosquitoes, perceptions about drone use for data collection, and acceptance of drones for *Aedes* mosquito surveillance around homes. Compared with people living in Turkey, Mexicans had 14.3 ( $p < 0.0001$ ) times higher odds and Malaysians had 4.0 ( $p = 0.7030$ ) times the odds of being willing to download a mosquito surveillance app. Compared to urban dwellers, rural dwellers had 1.56 times the odds of being willing to be trained. There is general community support for drone use in mosquito surveillance and this community buy-in suggests a potential for success in mosquito surveillance using drones. A successful surveillance and community engagement system

may be used to monitor a variety of mosquito spp. Future research should include qualitative interview data to add context to these findings.

### Dengue virus population genetics in Yogyakarta, Indonesia prior to city-wide Wolbachia deployment.

**Arguni, E., Indriani, C., Rahayu, A., Supriyati, E., Yohan, B., Hayati, R., Wardana, S., Tantowijoyo, W., Anshari, M., Rahayu, E., Rubangi, ., Ahmad, R., Utarini, A., Simmons, C., Sasmono, R.**  
26-05-2022

*Infect Genet Evol*

<https://pubmed.ncbi.nlm.nih.gov/35644356>

Dengue has been endemic in Yogyakarta, Indonesia for decades. Here, we report the dengue epidemiology, entomology, and virology in Yogyakarta in 2016-2017, prior to the commencement of the Applying Wolbachia to Eliminate Dengue (AWED) randomized trial. Dengue epidemiological data were compiled and blood samples from dengue-suspected patients were tested for dengue virus (DENV). *Ae. aegypti* mosquito samples were caught from the field using BG-Sentinel traps and tested for the presence of DENV infection. Sequencing of the DENV E gene was used to determine the phylogeny and genotypes of circulating DENV. Within the last decade, the 2016-2017 dengue incidence was considered very high. Among the 649 plasma samples collected between March 2016-February 2017; and 36,910 mosquito samples collected between December 2016-May 2017, a total of 197 and 38 samples were DENV-positive by qRT-PCR, respectively. All four DENV serotypes were detected, with DENV-3 ( $n = 88$ ; 44.67%) and DENV-1 ( $n = 87$ ; 44.16%) as the predominant serotype, followed by DENV-4 ( $n = 12$ ; 6.09%) and DENV-2 ( $n = 10$ ; 5.08%). The Yogyakarta DENV-1 isolates were classified into Genotype I and IV, while DENV-2, DENV-3, and DENV-4 isolates were classified into the Cosmopolitan genotype, Genotype I, and Genotype II, respectively. Yogyakarta DENV isolates were closely related to Indonesian strains from neighboring Javanese cities, consistent with the endemic circulation of DENV on this highly populous island. Our study provides comprehensive baseline information on the DENV population genetic characteristics in Yogyakarta, which are useful as baseline data for the AWED trial and the future DENV surveillance in the city in the presence of a *Wolbachia*-infected *Ae. aegypti* population.

### A conserved set of mutations for stabilizing soluble envelope protein dimers from Dengue and Zika viruses to advance the development of subunit vaccines.

**Phan, T., Hvasta, M., Kudlacek, S., Thiono, D., Tripathy, A., Nicely, N., de Silva, A., Kuhlman, B.**  
25-05-2022

*J Biol Chem*

<https://pubmed.ncbi.nlm.nih.gov/35643320>

Dengue viruses (DENV1-4) and Zika virus (ZIKV) are closely

related flaviviruses that continue to be a global public health concern, infecting hundreds of millions of people annually. The traditional live-attenuated virus vaccine approach has been challenging for the four DENV serotypes because of the need to achieve balanced replication of 4 independent vaccine components. Subunit vaccines represent an alternative approach that may circumvent problems inherent with tetravalent, live attenuated DENV vaccines. In mature virus particles, the envelope (E) protein forms a homodimer that covers the surface of the virus and is the major target of neutralizing antibodies. Many neutralizing antibodies bind to quaternary epitopes that span across both E proteins in the homodimer. For soluble E (sE) protein to be a viable subunit vaccine, the antigens should be easy to produce and retain quaternary epitopes recognized by neutralizing antibodies. However, wild type sE proteins are primarily monomeric at conditions relevant for vaccination and exhibit low expression yields. Previously, we used molecular modelling to identify amino acid mutations that stabilize the sE homodimer from DENV2 and dramatically raise expression yields. Here, we tested whether these same mutations raise the stability of sE from other DENV serotypes and ZIKV. We show that the mutations raise thermostability for sE from all of the viruses, increase production yields from 4-fold to 250-fold, stabilize the homodimer, and promote binding to dimer-specific neutralizing antibodies. Our findings suggest these sE variants could be valuable resources in the efforts to develop effective subunit vaccines for DENV1-4 and ZIKV.

### Hemin protects against Zika virus infection by disrupting virus-endosome fusion.

Xu, M., Wu, B., Huang, G., Feng, C., Wang, X., Wang, H., Wu, Y., Tang, W.

26-05-2022

*Antiviral Res*

<https://pubmed.ncbi.nlm.nih.gov/35643150>

Zika virus (ZIKV) is a flavivirus that causes severe neuropathology in newborns and adults. There is no ZIKV-specific treatment or preventative. Therefore, it is urgent to develop safe and effective anti-ZIKV agents. Hemin, an iron-binding porphyrin, has been authorized by FDA to treat acute porphyria since the 1970s. Here, we aim to evaluate the anti-ZIKV effect of hemin in SNB-19 cells (a human glioma cell line) and explore the underlying mechanism based on the virus life cycle and functions of the host cell. Our study found that hemin has a strong activity to protect SNB-19 cells from ZIKV infection presented by decreased expression of viral proteins and virus yield. Meanwhile, ZIKV infection caused STAT1/IRF1 signaling activation and induced inflammatory responses in SNB-19 cells, which was relieved by hemin treatment. HO-1 has been reported to be potentially induced by hemin and play a broad-spectrum antiviral effect. Intriguingly, hemin could still exert anti-ZIKV activity upon HO-1 siRNA treatment. Then, we conducted a time-of-addition assay, the result indicated hemin works mainly by interfering with the virus entry process. Further experiments excluded the effects of hemin on AXL-dependent viral adsorption and clathrin-mediated

endocytosis processes. Subsequently, by fluorescence spectroscopy studies, intracellular fusion assay and syncytia formation assay, we revealed that hemin acts on the process of virus-endosome fusion. This study elaborated that hemin could play anti-ZIKV activity by disrupting the virus-endosome fusion process and shed new light on developing novel agents against ZIKV infection.

### Etanercept for refractory chronic and deforming Chikungunya polyarthritis: a case report.

Bandeira, M., Dourado, E., Fonseca, J.

26-05-2022

*Rheumatology (Oxford)*

<https://pubmed.ncbi.nlm.nih.gov/35639642>

### Clinical Safety Experience of TAK-003 for Dengue Fever: a new Tetravalent Live Attenuated Vaccine Candidate.

Patel, S., Rauscher, M., Kudela, M., Pang, H.

26-05-2022

*Clin Infect Dis*

<https://pubmed.ncbi.nlm.nih.gov/35639602>

**Background:** An unmet medical need remains for an effective dengue tetravalent vaccine that can be administered irrespective of previous dengue exposure. TAK-003, a dengue tetravalent vaccine, has demonstrated efficacy in an ongoing phase 3 trial in children and adolescents living in dengue-endemic areas, with an acceptable safety profile in both dengue-naïve and -exposed individuals. **Methods:** Safety findings are presented herein from an integrated analysis of data for healthy 4-60-year-olds from two phase 2 and three phase 3 double-blind, placebo-controlled clinical trials of TAK-003 (TAK-003: n=14,627; placebo: n=7,167). Safety evaluation included analyses of post-injection reactogenicity, unsolicited adverse events (AEs), serious AEs (SAEs), and deaths. Subgroup analyses were performed by age group, baseline serostatus, and gender. **Results:** The most common local and systemic AEs were injection site pain (TAK-003: 43%; placebo: 26%) and headache (TAK-003: 34%; placebo: 30%). Injection site AEs were mostly mild and resolved within 1-3 days. Unsolicited AEs and AEs leading to discontinuation occurred with similar frequency across both groups, while SAEs were fewer for TAK-003 recipients (6% vs 8% placebo). Four of the five vaccine-related SAEs (which included hypersensitivity, dengue fever, and dengue hemorrhagic fever) occurred in the placebo group. No deaths were considered vaccine-related. Subgroup analyses showed no differences in safety by baseline serostatus or by gender, albeit analysis by age indicated greater local reactogenicity rates for adolescents (TAK-003: 46%; placebo: 28%) and adults (TAK-003: 56%, placebo: 19%) than for children (TAK-003: 37%, placebo: 25%). **Conclusion:** No important safety risks were identified, and TAK-003 was well-tolerated irrespective of age, gender, or baseline dengue serostatus in recipients aged 4-60 years.

### Perplexity as a provocation: revisiting the role of metaphor as a 'place holder' for the potential of COVID-19 antibodies.

Rosengarten, M.

30-05-2022

*Med Humanit*

<https://pubmed.ncbi.nlm.nih.gov/35636932>

This article revisits long-standing critiques of the role of metaphor in immunological discourse. Drawing on Alfred North Whitehead's speculative philosophy of organism, I focus on the use of metaphor to explain the process by which COVID-19 vaccine research is able to generate protective antibodies, the challenge of autoimmune disease and dengue fever antibodies. I suggest that metaphors are provoked by the perplexity that arises from presupposing that distinct morphological substances are the first order of reality. I conclude that rather than seeing metaphors as typically skewing conceptions of the body, as has been previously argued, those of memory, recognition and misrecognition may be instructive of a body in transition. Indeed, a process of transition that shows degrees of creativity. When gesturing towards the processual nature of infection and immunity, metaphors invite new modes of shared thinking across the disciplinary divide.

### Effect of sericin, a silk derived protein, on the amplification of Zika virus in insect and mammalian cell cultures.

Alcalá, A., Contreras, M., Cuevas-Juárez, E., Ramírez, O., Palomares, L.

24-05-2022

*J Biotechnol*

<https://pubmed.ncbi.nlm.nih.gov/35623476>

Sericin, a silk-derived non-immunogenic protein, has been used to improve cell culture performance by increasing viability, cell concentration, and promoting adherence of several cell lines. Here, we hypothesized that the properties of sericin can enhance the amplification of flaviviruses in cell cultures. The propagation of flavivirus is inefficient and limits scientific research. Zika virus (ZIKV) is an important human pathogen that has been widely studied because of its high impact on public health. There is a need to amplify Zika virus both for research and vaccine development. In this work, we show that sericin improves ZIKV amplification in insect (C6/36) and mammalian (VeroE6) cell cultures, and that it has a cryoprotectant capacity. Supplementation of cell culture media with sericin at 80µg/mL resulted in a significant increase of 1log in the concentration of ZIKV infectious particles produced from both cell lines. Furthermore, final virus yields increased between 5 to 10-fold in Vero cells and between 7 to 23-fold in C6/36 cells when sericin was supplemented, compared to control conditions. These results show that sericin is an effective supplement to increase ZIKV production by Vero and C6/36 cells. Additionally, sericin was a suitable cryoprotective agent, and hence an alternative to FBS and DMSO, for the cryopreservation of C6/36 cells but not for

Vero cells.

### Novel molecular approaches to combat vectors and vector-borne viruses: Special focus on RNA interference (RNAi) mechanisms.

Revue de littérature

Agarwal, A., Sarma, D., Chaurasia, D., Maan, H.

24-05-2022

*Acta Trop*

<https://pubmed.ncbi.nlm.nih.gov/35623398>

Vector-borne diseases, such as dengue, chikungunya, zika, yellow fever etc pose significant burden among the infectious diseases globally, especially in tropical and sub-tropical regions. Globalization, deforestation, urbanization, climate change, uncontrolled population growth, inadequate waste management and poor vector-management infrastructure have all contributed to the expansion of vector habitats and subsequent increase in vector-borne diseases throughout the world. Conventional vector control methods, such as use of insecticides, have significant negative environmental repercussions in addition to developing resistance in vectors. Till date, a very few vaccines or antiviral therapies have been approved for the treatment of vector borne diseases. In this review, we have discussed emerging molecular approaches like CRISPR (clustered regularly interspaced short palindromic repeats)/Cas-9, sterile insect technique (SIT), release of insects carrying a dominant lethal (RIDL), Wolbachia (virus transmission blocking) and RNA interference (RNAi) to combat vector and vector-borne viruses. Due to the extensive advancements in RNAi research, a special focus has been given on its types, biogenesis, mechanism of action, delivery and experimental studies evaluating their application as anti-mosquito and anti-viral agent. These technologies appear to be highly promising in terms of contributing to vector control and antiviral drug development, and hence can be used to reduce global vector and vector-borne disease burden.

### Mammalian viral suppressors of RNA interference.

Revue de littérature

Li, W., Ding, S.

23-05-2022

*Trends Biochem Sci*

<https://pubmed.ncbi.nlm.nih.gov/35618579>

The antiviral defense directed by the RNAi pathway employs distinct specificity and effector mechanisms compared with other immune responses. The specificity of antiviral RNAi is programmed by siRNAs processed from virus-derived double-stranded RNA by Dicer endonuclease. Argonaute-containing RNA-induced silencing complex loaded with the viral siRNAs acts as the effector to mediate specific virus clearance by RNAi. Recent studies have provided evidence for the production and antiviral function of virus-derived siRNAs in both undifferentiated and differentiated mammalian cells infected with a range of RNA viruses when the cognate virus-encoded suppressor of RNAi (VSR) is rendered nonfunctional.

In this review, we discuss the function, mechanism, and evolutionary origin of the validated mammalian VSRs and cell culture assays for their identification.

### The discovery of Zika virus NS2B-NS3 inhibitors with antiviral activity via an integrated virtual screening approach.

Mirza, M., Alanko, I., Vanmeert, M., Muzzarelli, K., Salo-Ahen, O., Abdullah, I., Kovari, I., Claes, S., De Jonghe, S., Schols, D., Schinazi, R., Kovari, L., Trant, J., Ahmad, S., Froeyen, M.  
23-05-2022

*Eur J Pharm Sci*

<https://pubmed.ncbi.nlm.nih.gov/35618201>

With expanding recent outbreaks and a lack of treatment options, the Zika virus (ZIKV) poses a severe health concern. The availability of ZIKV NS2B-NS3 co-crystallized structures paved the way for rational drug discovery. A computer-aided structure-based approach was used to screen a diverse library of compounds against ZIKV NS2B-NS3 protease. The top hits were selected based on various binding free energy calculations followed by per-residue decomposition analysis. The selected hits were then evaluated for their biological potential with ZIKV protease inhibition assay and antiviral activity. Among 26 selected compounds, 8 compounds showed promising activity against ZIKV protease with a percentage inhibition of greater than 25 and 3 compounds displayed ~50% at 10  $\mu$ M, which indicates an enrichment rate of approximately 36% (threshold  $IC_{50} < 10 \mu$ M) in the ZIKV-NS2B-NS3 protease inhibition assay. Of these, only one compound (23) produced whole-cell anti-ZIKV activity, and the binding mode of 23 was extensively analyzed through long-run molecular dynamics simulations. The current study provides a promising starting point for the further development of novel compounds against ZIKV.

### Cross-reactive antibodies targeting surface-exposed non-structural protein 1 (NS1) of dengue virus-infected cells recognize epitopes on the spaghetti loop of the $\beta$ -ladder domain.

Kraivong, R., Traewachiwiphak, S., Nilchan, N., Tangthawornchaikul, N., Pornmun, N., Poraha, R., Sriruksa, K., Limpitikul, W., Avirutnan, P., Malasit, P., Puttikhunt, C.  
26-05-2022

*PLoS One*

<https://doi.org/10.1371/journal.pone.0266136>

Non-structural protein 1 (NS1) is a glycoprotein component of dengue virus (DENV) that is essential for viral replication, infection and immune evasion. Immunization with NS1 has been shown to elicit antibody-mediated immune responses which protect mice against DENV infections. Here, we obtained peripheral blood mononuclear cells from human subjects with secondary dengue infections, which were used to construct a dengue immune phage library displaying single-chain variable fragments. Phage selective for DENV NS1 were obtained by biopanning. Twenty-one monoclonal antibodies

(mAbs) against DENV NS1 were generated from the selected phage and characterized in detail. We found most anti-NS1 mAbs used IGHV1 heavy chain antibody genes. The mAbs were classified into strongly and weakly-reactive groups based on their binding to NS1 expressed in dengue virus 2 (DENV2)-infected cells. Antibody binding experiments with recombinant NS1 proteins revealed that the mAbs recognize conformational epitopes on the  $\beta$ -ladder domain (amino acid residues 178-273) of DENV NS1. Epitope mapping studies on alanine-substituted NS1 proteins identified distinct but overlapping epitopes. Protruding amino acids distributed around the spaghetti loop are required for the binding of the strongly-reactive mAbs, whereas the recognition residues of the weakly-reactive mAbs are likely to be located in inaccessible sites facing toward the cell membrane. This information could guide the design of an NS1 epitope-based vaccine that targets cross-reactive conserved epitopes on cell surface-associated DENV NS1.

### Factors related to the quality of life of mothers of children with Congenital Zika Virus Syndrome.

Ortoni, G., Rocha, A., Veríssimo, T., Moreira, M., Ribeiro, M., Prudente, C.  
23-05-2022

*Rev Gaucha Enferm*

<https://pubmed.ncbi.nlm.nih.gov/35613228>

**Objective:** To relate sociodemographic and clinical aspects to the quality of life of mothers of children with Congenital Zika Virus Syndrome. **Method:** Cross-sectional analytical study, conducted in a rehabilitation center in Goiânia, central region of Brazil. A sociodemographic and clinical profile questionnaire and the World Health Organization Quality of Life were used. Data analysis was performed using the Mann-Whitney tests; Kruskal-Wallis, followed by Dunnett's Post hoc; and Spearman's correlation. **Results:** The sample consisted of 30 mothers of children with Congenital Zika Virus Syndrome, with a mean age of  $30.57 \pm 6.67$  years. Mothers who had a partner, leisure activity, who used a car as a means of transport and who had a child with congenital syndrome with microcephaly had a better quality of life ( $p < 0,05$ ). **Conclusion:** The quality of life of these mothers was related to sociodemographic and clinical aspects, which suggests the need for more specific public policies for this population.

### A prospective observational study of community-acquired bacterial bloodstream infections in Metro Manila, the Philippines.

Saito, N., Solante, R., Guzman, F., Telan, E., Umipig, D., Calayo, J., Frayco, C., Lazaro, J., Ribo, M., Dimapilis, A., Dimapilis, V., Villanueva, A., Mauhay, J., Suzuki, M., Yasunami, M., Koizumi, N., Kitashoji, E., Sakashita, K., Yasuda, I., Nishiyama, A., Smith, C., Ariyoshi, K., Parry, C.  
25-05-2022

*PLoS Negl Trop Dis*

<https://doi.org/10.1371/journal.pntd.0010414>

Community-acquired bacterial bloodstream infections are

caused by diverse pathogens with changing antimicrobial-resistance patterns. In low-middle income countries in Southeast Asia, where dengue fever is endemic and a leading cause of fever, limited information is available about bacterial bloodstream infections due to challenges of implementing a blood culture service. This study describes bacterial bloodstream pathogens and antimicrobial-resistance patterns in Metro Manila, the Philippines. We aimed to identify the proportion of patients with a positive blood culture, the bacteria isolated and their antimicrobial resistance patterns, and the clinical characteristics of these patients, in this dengue endemic area. We conducted a prospective observational study in a single hospital enrolling febrile patients clinically suspected of having a community-acquired bacterial bloodstream infection between 1st July 2015 and 30th June 2019. Each patient had a blood culture and additional diagnostic tests according to their clinical presentation. We enrolled 1315 patients and a significant positive blood culture was found in 77 (5.9%) including *Staphylococcus aureus* (n = 20), *Salmonella enterica* Typhi (n = 18), *Escherichia coli* (n = 16), *Streptococcus pneumoniae* (n = 3) and *Burkholderia pseudomallei* (n = 2). Thirty-four patients had meningococcal disease diagnosed by culture (n = 8) or blood PCR (n = 26). Additional confirmed diagnoses included leptospirosis (n = 177), dengue virus infection (n = 159) and respiratory diphtheria (n = 50). There were 79 (6.0%, 95%CI 4.8%-7.4%) patients who died within 28 days of enrollment. Patients with a positive blood culture were significantly more likely to die than patients with negative culture (15.2% vs 4.4%,  $P < 0.01$ ). Among *S. aureus* isolates, 11/20 (55%) were methicillin-resistant (MRSA) and ST30: USA1100 was dominant sequence type (88.9%). Antimicrobial-susceptibility was well preserved in *S. enterica* Typhi. Among hospitalized patients with clinically suspected community-acquired bacterial bloodstream infection in Metro Manila, the Philippines, 5.9% had a blood culture confirmed infection of whom 15.6% died. *S. aureus*, including a significant number of MRSA (USA1100 clones), *S. enterica* Typhi, *E. coli* and *Neisseria meningitidis* were frequently identified pathogens.

### Antiviral Activity of Rosmarinic Acid Against Four Serotypes of Dengue Virus.

Panchal, R., Ghosh, S., Mehla, R., Ramalingam, J., Gairola, S., Mukherjee, S., Chowdhary, A.

25-05-2022

*Curr Microbiol*

<https://doi.org/10.1007/s00284-022-02889-3>

The present study was undertaken to evaluate the putative antiviral activity of Rosmarinic acid (RA) against four serotypes of dengue virus (DENV). Our previous *in silico* binding analysis revealed that RA binds strongly to the envelope domain III (EDIII) protein of all four DENV serotypes. We employed an *in vitro* Biolayer Interferometry-based OCTET™ platform to study the binding interaction of RA with EDIII protein of the four DENV serotypes. Additionally, a functional plaque assay was developed to investigate the potential inhibition of infection of the four DENV serotypes. Using OCTET™, the binding

interaction of RA to DENV-EDIII protein of the four DENV serotypes demonstrates interaction which can be arranged in the following order: EDIII-DENV1 ( $K_{off}$  value of  $1.05 \text{ s}^{-1}$ ) > EDIII-DENV2 ( $K_{off}$  value of  $5.63 \times 10^{-01} \text{ s}^{-1}$ ) > EDIII-DENV3 ( $K_{off}$  value of  $4.63 \times 10^{-02} \text{ s}^{-1}$ ) > EDIII-DENV4 ( $K_{off}$  value of  $3.53 \times 10^{-02} \text{ s}^{-1}$ ). Subsequently, the inhibiting ability of RA using plaque assay confirmed reduction in the number of plaques for all four serotypes, indicating the ability of RA not only to bind, but also to inhibit the infection of four serotypes in cell culture, while being non-toxic at the concentrations used in the study. However, the effect of RA was variable on different serotypes, demonstrating highest effect on DENV1 ( $EC_{50} = 13.73 \text{ } \mu\text{g/mL}$ ,  $SI \geq 728$ ) followed by DENV2 ( $EC_{50} = 77.74 \text{ } \mu\text{g/mL}$ ,  $SI \geq 129$ ), DENV3 ( $EC_{50} = 244 \text{ } \mu\text{g/mL}$ ,  $SI \geq 41$ ) and DENV4 ( $EC_{50} = 280 \text{ } \mu\text{g/mL}$ ,  $SI \geq 36$ ).

### Identification and characterization of key residues in Zika virus envelope protein for virus assembly and entry.

Ma, X., Yuan, Z., Yi, Z.

25-05-2022

*Emerg Microbes Infect*

<https://doi.org/10.1080/22221751.2022.2082888>

Zika virus (ZIKV), a family member in the *Flavivirus* genus, has re-emerged as a global public health concern. The envelope (E) proteins of flaviviruses play a dual role in viral assembly and entry. To identify the key residues of E in virus entry, we generated a ZIKV *trans*-complemented particle (ZIKV<sub>TCP</sub>) system, in which a subgenomic reporter replicon was packaged by *trans*-complementation with expression of CprME. We performed mutagenesis studies of the loop regions that protrude from the surface of the virion in the E ectodomains (DI, DII, DIII). Most mutated ZIKV<sub>TCPs</sub> exhibited deficient egress. Mutations in DII and in the hinge region of DI and DIII affected prM expression. With a bioorthogonal system, photocrosslinking experiments identified crosslinked intracellular E trimers and demonstrated that egress-deficient mutants in DIII impaired E trimerization. Of these mutants, an E-trimerization-dead mutation D389A that nears the E-E interface between two neighboring spikes in the immature virion completely abolished viral egress. Several mutations abolished ZIKV<sub>TCPs</sub>' entry, without severely affecting viral egress. Further virus binding experiments demonstrated a deficiency of the mutated ZIKV<sub>TCPs</sub> in virus attachment. Strikingly, synthesized peptide containing residues of two mutants (268-273aa in DII) could bind to host cells and significantly compete for viral attachment and interfere with viral infection, suggesting an important role of these residues in virus entry. Our findings uncovered requirement for DIII mediated-E trimerization in viral egress, and discovered a key residue group in DII that participates in virus entry.

### The Tetraspanin CD81 Is a Host Factor for Chikungunya Virus Replication.

Lasswitz, L., Zapatero-Belinchón, F., Moeller, R., Hülskötter, K., Laurent, T., Carlson, L., Goffinet, C., Simmons, G., Baumgärtner,

W., Gerold, G.

25-05-2022

mBio

<https://doi.org/10.1128/mbio.00731-22>

Chikungunya virus (CHIKV) is an arthritogenic reemerging virus replicating in plasma membrane-derived compartments termed "spherules." Here, we identify the human transmembrane protein CD81 as host factor required for CHIKV replication. Ablation of CD81 results in decreased CHIKV permissiveness, while overexpression enhances infection. CD81 is dispensable for virus uptake but critically required for viral genome replication. Likewise, murine CD81 is crucial for CHIKV permissiveness and is expressed in target cells such as dermal fibroblasts, muscle and liver cells. Whereas related alphaviruses, including Ross River virus (RRV), Semliki Forest virus (SFV), Sindbis virus (SINV) and Venezuelan equine encephalitis virus (VEEV), also depend on CD81 for infection, RNA viruses from other families, such as coronaviruses, replicate independently of CD81. Strikingly, the replication-enhancing function of CD81 is linked to cholesterol binding. These results define a mechanism exploited by alphaviruses to hijack the membrane microdomain-modeling protein CD81 for virus replication through interaction with cholesterol.

**IMPORTANCE** In this study, we discover the tetraspanin CD81 as a host factor for the globally emerging chikungunya virus and related alphaviruses. We show that CD81 promotes replication of viral genomes in human and mouse cells, while virus entry into cells is independent of CD81. This provides novel insights into how alphaviruses hijack host proteins to complete their life cycle. Alphaviruses replicate at distinct sites of the plasma membrane, which are enriched in cholesterol. We found that the cholesterol-binding ability of CD81 is important for its function as an alphavirus host factor. This discovery thus broadens our understanding of the alphavirus replication process and the use of host factors to reprogram cells into virus replication factories.

### Dengue Vaccines: An Update.

Torres-Flores, J., Reyes-Sandoval, A., Salazar, M.

24-05-2022

BioDrugs

<https://doi.org/10.1007/s40259-022-00531-z>

Dengue is one of the most prevalent mosquito-borne diseases in the world, affecting an estimated 390 million people each year, according to models. For the last two decades, efforts to develop safe and effective vaccines to prevent dengue virus (DENV) infections have faced several challenges, mostly related to the complexity of conducting long-term studies to evaluate vaccine efficacy and safety to rule out the risk of vaccine-induced DHS/DSS, particularly in children. At least seven DENV vaccines have undergone different phases of clinical trials; however, only three of them (Dengvaxia®, TV003, and TAK-003) have showed promising results, and are addressed in detail in this review in terms of their molecular design, efficacy, and immunogenicity. Safety-related challenges during DENV vaccine development are also discussed.

### Temephos, an organophosphate larvicide for residential use: a review of its toxicity.

Revue de littérature

Martínez-Mercado, J., Sierra-Santoyo, A., Verdín-Betancourt, F., Rojas-García, A., Quintanilla-Vega, B.

24-05-2022

Crit Rev Toxicol

<https://doi.org/10.1080/10408444.2022.2065967>

Temephos (*O,O,O',O'*-tetramethyl *O,O'*-thiodi-*p*-phenylene bis(phosphorothioate)) is a larvicide belonging to the family of organophosphate pesticides used for the control of different vectors of diseases, such as dengue, Zika, chikungunya, and dracunculiasis. The aim of this review was to discuss the available published information about temephos toxicokinetics and toxicity in mammals. Temephos is quickly absorbed in the gastrointestinal tract, distributed to all organs, and then it accumulates mainly in adipose tissue. It is metabolized by *S*-oxidation, oxidative desulfuration, and hydrolysis reactions, with the possible participation of cytochrome P450 (CYP). Temephos is mainly eliminated by feces, whereas some of its metabolites are eliminated by urine. The World Health Organization classifies it as class III: slightly dangerous with a NOAEL (no-observed adverse effect level) of 2.3 mg/kg/day for up to 90 days in rats, based on brain acetylcholinesterase (AChE) inhibition. A LOAEL (lowest observable adverse effect level) of 100 mg/kg/day for up to 44 days in rats was proposed based on cholinergic symptoms. However, some studies have shown that temephos causes toxic effects in mammals. The inhibition of the enzyme acetylcholinesterase (AChE) is one of its main demonstrated effects; however, this larvicide has also shown genotoxic effects and some adverse effects on male reproduction and fertility, as well as liver damage, even at low doses. We performed an extensive review through several databases of the literature about temephos toxicokinetics, and we recommend to revisit current assessment of temephos with the new available data.

### Dengue virus NS1 protein conveys pro-inflammatory signals by docking onto high-density lipoproteins.

Benfrid, S., Park, K., Dellarole, M., Voss, J., Tamiatti, C., Pehau-Arnaudet, G., Raynal, B., Brûlé, S., England, P., Zhang, X., Mikhailova, A., Hasan, M., Ungeheuer, M., Petres, S., Biering, S., Harris, E., Sakuntabhai, A., Buchy, P., Duong, V., Dussart, P., Coulibaly, F., Bontems, F., Rey, F., Flamand, M.

24-05-2022

EMBO Rep

<https://doi.org/10.15252/embr.202153600>

The dengue virus nonstructural protein 1 (NS1) is a secreted virulence factor that modulates complement, activates immune cells and alters endothelial barriers. The molecular basis of these events remains incompletely understood. Here we describe a functional high affinity complex formed between NS1 and human high-density lipoproteins (HDL). Collapse of the soluble NS1 hexamer upon binding to the

lipoprotein particle leads to the anchoring of amphipathic NS1 dimeric subunits into the HDL outer layer. The stable complex can be visualized by electron microscopy as a spherical HDL with rod-shaped NS1 dimers protruding from the surface. We further show that the assembly of NS1-HDL complexes triggers the production of pro-inflammatory cytokines in human primary macrophages while NS1 or HDL alone do not. Finally, we detect NS1 in complex with HDL and low-density lipoprotein (LDL) particles in the plasma of hospitalized dengue patients and observe NS1-apolipoprotein E-positive complexes accumulating overtime. The functional reprogramming of endogenous lipoprotein particles by NS1 as a means to exacerbate systemic inflammation during viral infection provides a new paradigm in dengue pathogenesis.

### **A dengue-like outbreak of unknown aetiology in Pakistan.**

**Merchant, H.**

23-05-2022

*Trop Med Health*

<https://doi.org/10.1186/s41182-022-00426-3>

There were recent reports of a mysterious virus spreading in Pakistan causing dengue-like illness with hundreds of cases admitted to hospitals over the winter. The mysterious virus was touted as a new variant of the dengue virus by the local health experts in Pakistan as most patients were tested negative for the dengue virus test despite presenting with dengue-like symptoms. In this letter, we have critically appraised the current situation in Pakistan in an attempt to explain the science and mechanism behind recent dengue-like outbreak, offered suggestions on diagnostic tests and provided recommendations to improve medication safety in Pakistan.

### **Electrochemical and DFT studies of andrographolide on electrochemically reduced graphene oxide for anti-viral herbaceutical sensor.**

**Kanagavalli, P., Pandey, G., Murugan, P., Veerapandian, M.**

25-04-2022

*Anal Chim Acta*

<https://pubmed.ncbi.nlm.nih.gov/35569854>

Herbal extracts are re-emerging as potential remedies for various vector-borne diseases. Amongst several phytochemicals, active ingredients of *Andrographis paniculata* extract is regarded as promising for dengue fever, caused by *Aedes* species. However, fingerprinting the active phytochemicals from herbal extracts are often relies on sophisticated analytical techniques which are not universally accessible. Herein, an electrochemically reduced graphene oxide on glassy carbon electrode (ErGO/GCE) has been devised as user-friendly and cost-effective sensor platform for fingerprinting of andrographolide (AG) in anti-dengue polyherbal formulation, i.e., Nilavembu kudineer powder. Confocal laser Raman and X-ray photoelectron spectral analyses revealed that the ErGO surfaces exert structural

defects augmenting the conductivity at the electrode interface. DFT investigations enabled that C-3 and C-18 OH groups in AG is involved in the electrooxidation and adsorption-diffusion at the ErGO interface, respectively. Complementary electrochemical studies revealed that the diffusion-controlled process follows  $1e^-/1H^+$  transfer. Under optimal experimental conditions, ErGO sensor platform exhibit an amplified current sensitivity of  $13.3 \mu A \mu M^{-1} cm^{-2}$  in the studied analyte concentration range of 10-400  $\mu M$ . From the polyherbal extract and clinical sample analysis, the proposed sensor system offers selective, and sensitive detection of target AG regardless of common interferents.

### **Vitamin D-induced LL-37 modulates innate immune responses of human primary macrophages during DENV-2 infection.**

**Castillo, J., Giraldo, D., Smit, J., Rodenhuis-Zybert, I., Urcuqui-Inchima, S.**

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*Pathog Dis*

<https://pubmed.ncbi.nlm.nih.gov/35512569>

Epidemics of dengue, an acute and potentially severe disease caused by mosquito-borne dengue virus (DENV), pose a major challenge to clinicians and health care services across the sub(tropics). Severe disease onset is associated with a dysregulated inflammatory response to the virus, and there are currently no drugs to alleviate disease symptoms. LL-37 is a potent antimicrobial peptide with a wide range of immunoregulatory properties. In this study, we assessed the effect of LL-37 on DENV-2-induced responses in human monocyte-derived macrophages (MDMs). We show that simultaneous exposure of exogenous LL-37 and DENV-2 resulted in reduced replication of the virus in MDMs, while the addition of LL-37 postexposure to DENV-2 did not. Interestingly, the latter condition reduced the production of IL-6 and increased the expression of genes involved in virus sensing and antiviral response. Finally, we demonstrate that low endogenous levels and limited production of LL-37 in MDMs in response to DENV-2 infection can be increased by differentiating MDMs in the presence of Vitamin D (VitD3). Taken together, this study demonstrates that in addition to its antimicrobial properties, LL-37 has immunomodulatory properties in the course of DENV infection and its production can be increased by VitD3.

### **Temperate Conditions Limit Zika Virus Genome Replication.**

**Tesla, B., Powers, J., Barnes, Y., Lakhani, S., Acciani, M., Brindley, M.**

25-04-2022

*J Virol*

<https://doi.org/10.1128/jvi.00165-22>

Zika virus is a mosquito-borne flavivirus known to cause severe birth defects and neuroimmunological disorders. We have previously demonstrated that mosquito transmission of

Zika virus decreases with temperature. While transmission was optimized at 29°C, it was limited at cool temperatures (<22°C) due to poor virus establishment in the mosquitoes. Temperature is one of the strongest drivers of vector-borne disease transmission due to its profound effect on ectothermic mosquito vectors, viruses, and their interaction. Although there is substantial evidence of temperature effects on arbovirus replication and dissemination inside mosquitoes, little is known about whether temperature affects virus replication directly or indirectly through mosquito physiology. In order to determine the mechanisms behind temperature-induced changes in Zika virus transmission potential, we investigated different steps of the virus replication cycle in mosquito cells (C6/36) at optimal (28°C) and cool (20°C) temperatures. We found that the cool temperature did not alter Zika virus entry or translation, but it affected genome replication and reduced the amount of double-stranded RNA replication intermediates. If replication complexes were first formed at 28°C and the cells were subsequently shifted to 20°C, the late steps in the virus replication cycle were efficiently completed. These data suggest that cool temperature decreases the efficiency of Zika virus genome replication in mosquito cells. This phenotype was observed in the Asian lineage of Zika virus, while the African lineage Zika virus was less restricted at 20°C. **IMPORTANCE** With half of the human population at risk, arboviral diseases represent a substantial global health burden. Zika virus, previously known to cause sporadic infections in humans, emerged in the Americas in 2015 and quickly spread worldwide. There was an urgent need to better understand the disease pathogenesis and develop therapeutics and vaccines, as well as to understand, predict, and control virus transmission. In order to efficiently predict the seasonality and geography for Zika virus transmission, we need a deeper understanding of the host-pathogen interactions and how they can be altered by environmental factors such as temperature. Identifying the step in the virus replication cycle that is inhibited under cool conditions can have implications in modeling the temperature suitability for arbovirus transmission as global environmental patterns change. Understanding the link between pathogen replication and environmental conditions can potentially be exploited to develop new vector control strategies in the future.

### Identification of Montelukast as flavivirus NS2B-NS3 protease inhibitor by inverse virtual screening and experimental validation.

Jiang, H., Zhang, Y., Wu, Y., Cheng, J., Feng, S., Wang, J., Wang, X., Cheng, M.

15-03-2022

*Biochem Biophys Res Commun*

<https://pubmed.ncbi.nlm.nih.gov/35339757>

Flavivirus, such as Dengue Virus (DENV) and Zika virus (ZIKV), infects millions of people and cause the death of thousands of people every year. Despite many efforts, there is no approved anti-flaviviral treatment available. In particular, some antiflavivirus compounds were investigated the cellular

activities of DENV and ZIKV, but lacking the exploration of specific target enzyme, thereby resulting in the hindrance of structure-based drug design. One example is Montelukast, which was found to inhibit the replicon replication in DENV and ZIKV infected cells, with EC<sub>50</sub> values as 1.03 μM (DENV) and 1.14 μM (ZIKV), while the underlying mechanism remains unclear. In our study, the inhibitory mechanisms of Montelukast against the replicon replication of DENV and ZIKV infected cells were studied by using in silico approaches including inverse virtual screening (IVS), molecular dynamics (MD) simulations and binding free energy calculation, and validated through in vitro protease assay, confirming Montelukast could bind to NS2B-NS3 proteases of DENV and ZIKV as a competitive inhibitor (IC<sub>50</sub> for DENV: 25.65 μM, for ZIKV: 15.57 μM). Moreover, Montelukast has no potential off-target effect on NS2B-NS3 protease from thrombin and trypsin inhibitory assay. Overall, Montelukast may be used as a potential candidate to block NS2B-NS3 protease as well as lead for structural modification.

### The Factors Associated with Prevention and Control Practices against Zika Virus Infection among Pregnant Women in Malaysia, a Dengue-Endemic Country.

Wong, L., Alias, H., Hassan, J., AbuBakar, S.

30-09-2021

*Jpn J Infect Dis*

<https://doi.org/10.7883/yoken.JJID.2021.342>

The aim of this study was to analyze the prevention and control practices against Zika virus (ZIKV) infection among pregnant women in Malaysia. A cross-sectional study was conducted among pregnant women who received antenatal care. Only 7.8% reported that they abstained from sex or used barrier methods during sexual intercourse to prevent ZIKV transmission. The odds of abstaining from sex or using barrier methods were significantly higher among the Chinese ethnic group than the Malay ethnic group (odds ratio [OR] = 4.569; 95% confidence interval [CI]: 2.696-7.743). A total ZIKV knowledge score of 12-24 was also significantly associated with higher odds of abstaining from sex or using barrier methods than a score of 0-11 (OR = 2.819; 95% CI: 1.682-4.725). In total, 38.6% of women had a higher mean total score for all the current mosquito control practices than they did before hearing of ZIKV. Participants living in bungalows or village houses (OR = 2.006; 95% CI: 1.023-3.936) and low-rise houses (OR = 1.566; 95% CI: 1.109-2.212) were more likely to have a higher mean total score of current mosquito control practices than the practices before hearing of ZIKV compared to those in high-rise houses. The lack of ZIKV knowledge and control practices provides insight for the pre-emptive and prompt development of health education systems for pregnant women during antenatal care visits.

### Predictive Analysis of Gallbladder Wall Thickness as a Marker for Bleeding Risk and Need for Transfusion in Dengue Patients.

**Asgar, M., Yasmin, F., Tahir, M., Anwar, S., Yaseen, R., Yousaf, Z.**

30-09-2021

*Jpn J Infect Dis*

<https://doi.org/10.7883/yoken.JJID.2021.076>

Increased gallbladder wall thickening (GBWT) is a manifestation of increased capillary permeability caused by severe dengue. This study was carried out to link the severity of GBWT with bleeding risk and the need for transfusion. This retrospective study included all patients diagnosed with dengue infection either via dengue nonstructural protein-1 antigen or IgM antibody. Pearson's correlation, linear regression, and receiver operating characteristic curves were used for predictive analysis of GBWT with events of bleeding and need for transfusion of platelets during the hospital stay. A total of 177 participants met the inclusion criteria; the mean age was  $33.17 \pm 13.63$  years. Mean GBWT was found to be  $0.37 \pm 0.15$  cm, with 46.3% of patients having a thickness greater than 0.30 cm. A total of 16 patients had bleeding events, of which 7.3% had minor bleeding and 1.7% had a major bleeding event. Linear regression analysis showed that increased GBWT was associated with decreased platelet count on admission ( $P = 0.002$ ) and lowest platelet counts ( $P = 0.004$ ). GBWT was found to be predictive of bleeding events and transfusion of platelets at higher sensitivity and specificity than was either platelet count on admission and lowest platelet counts.

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## RAGE

### Wrangling rabies.

**McKay, A.**

30-05-2022

*Nat Ecol Evol*

<https://doi.org/10.1038/s41559-022-01802-2>

### Covariation between glucocorticoids, behaviour and immunity supports the pace-of-life syndrome hypothesis: an experimental approach.

**Carbillet, J., Rey, B., Palme, R., Monestier, C., Börger, L., Lavabre, T., Maublanc, M., Cebe, N., Rames, J., Le Loc'h, G., Wasniewski, M., Rannou, B., Gilot-Fromont, E., Verheyden, H.**

25-05-2022

*Proc Biol Sci*

<https://doi.org/10.1098/rspb.2022.0464>

The biomedical literature has consistently highlighted that long-term elevation of glucocorticoids might impair immune functions. However, patterns are less clear in wild animals. Here, we re-explored the stress-immunity relationship considering the potential effects of behavioural profiles. Thirteen captive roe deer (*Capreolus capreolus*) were monitored over an eight-week period encompassing two

capture events. We assessed how changes in baseline faecal cortisol metabolite (FCM) concentrations following a standardized capture protocol and an immune challenge using anti-rabies vaccination affected changes in 13 immune parameters of innate and adaptive immunity, and whether these changes in baseline FCM levels and immune parameters related to behavioural profiles. We found that individuals with increased baseline FCM levels also exhibited increased immunity and were characterized by more reactive behavioural profiles (low activity levels, docility to manipulation and neophilia). Our results suggest that the immunity of large mammals may be influenced by glucocorticoids, but also behavioural profiles, as it is predicted by the pace-of-life syndrome hypothesis. Our results highlight the need to consider covariations between behaviour, immunity and glucocorticoids in order to improve our understanding of the among-individual variability in the stress-immunity relationships observed in wildlife, as they may be underpinned by different life-history strategies.

### Single-cell transcriptomic classification of rabies-infected cortical neurons.

**Patiño, M., Lagos, W., Patne, N., Tasic, B., Zeng, H., Callaway, E.**

24-05-2022

*Proc Natl Acad Sci U S A*

<https://doi.org/10.1073/pnas.2203677119>

Significance Monosynaptic rabies tracing using glycoprotein (G)-deleted rabies virus is widely applied to study cortical circuit connectivity. However, connectivity tracing using rabies virus could benefit from higher throughput methods of assigning rabies-labeled inputs to neuronal cell types and the ability to assign cells to finer genetically defined subtypes. Using single-nucleus RNA sequencing, we demonstrate that rabies-infected cortical neurons can be transcriptomically characterized according to established cell types when using transcriptome-wide analysis. Furthermore, we find that rabies infection differentially affects distinct host genes, suggesting that some genes may be more vulnerable to transcriptional modulation than others, which may impede the classification of rabies-infected cells when using methods that rely on the detection of single or few genes.

### [The Greek-Roman physician Galen of Pergamum and his neurological case histories].

Revue de littérature

**Golder, W.**

23-05-2022

*Nervenarzt*

<https://doi.org/10.1007/s00115-022-01316-z>

**Background:** The case histories in the writings of Galen of Pergamum have so far been interpreted primarily in literary and socio-historic terms. The analysis focused on the medical aspects is still incomplete. **Question:** Which neurological competences do the galenic case reports communicate?

**Material and methods:** The 400 galenic case histories were

studied for anamnestic, clinical, therapeutic, and prognostic statements on neurological and psychiatric diseases. **Results:** In about every tenth case report, neurological and/or psychiatric disorders are discussed. Most of them are found in the works Anatomical procedures, On the affected parts and Method of Healing. Both individual patients and patient groups are reported. The author calls prominent patients by name. The descriptions do not follow a fixed structure. The texts are governed by information on the anamnesis and catamnesis and the results of the physical examination. The author has repeatedly combined the description of the individual cases with theoretical remarks. The most common diseases of the nervous system Galen encountered were traumatic palsy, paresthesia, incontinence, rabies, epilepsy, depression and insanity. Symptoms associated with fever and epidemics also played an important role. In most cases, Galen was the attending physician. Secondhand medical histories are also told. The most invasive treatment procedure was trepanation. **Discussion:** The case reports cover much of the spectrum of diseases of the nervous system mentioned by Galen. The doctor-patient tales are the most ingenious element in terms of style and content. The often sparse statements on the choice of treatment show that the ancient doctor hardly had any specific measures available for patients suffering from neurologic diseases with the exception of the rarely indicated and practiced surgical interventions.

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## TRACHOME

### Trachoma.

26-05-2022

*Nat Rev Dis Primers*
<https://doi.org/10.1038/s41572-022-00369-3>

### Trachoma.

Revue de littérature

**Solomon, A., Burton, M., Gower, E., Harding-Esch, E., Oldenburg, C., Taylor, H., Traoré, L.**

26-05-2022

*Nat Rev Dis Primers*
<https://doi.org/10.1038/s41572-022-00359-5>

Trachoma is a neglected tropical disease caused by infection with conjunctival strains of *Chlamydia trachomatis*. It can result in blindness. Pathophysiologically, trachoma is a disease complex composed of two linked chronic processes: a recurrent, generally subclinical infectious-inflammatory disease that mostly affects children, and a non-communicable, cicatricial and, owing to trichiasis, eventually blinding disease that supervenes in some individuals later in life. At least 150 infection episodes over an individual's lifetime are needed to precipitate trichiasis; thus, opportunity exists for a just global

health system to intervene to prevent trachomatous blindness. Trachoma is found at highest prevalence in the poorest communities of low-income countries, particularly in sub-Saharan Africa; in June 2021, 1.8 million people worldwide were going blind from the disease. Blindness attributable to trachoma can appear in communities many years after conjunctival *C. trachomatis* transmission has waned or ceased; therefore, the two linked disease processes require distinct clinical and public health responses. Surgery is offered to individuals with trichiasis and antibiotic mass drug administration and interventions to stimulate facial cleanliness and environmental improvement are designed to reduce infection prevalence and transmission. Together, these interventions comprise the SAFE strategy, which is achieving considerable success. Although much work remains, a continuing public health problem from trachoma in the year 2030 will be difficult for the world to excuse.

### Fluorescent Biosensor Based on Hairpin DNA Stabilized Copper Nanoclusters for *Chlamydia trachomatis* Detection.

**Liu, L., Bai, Q., Zhang, X., Lu, C., Li, Z., Liang, H., Chen, L.**

25-05-2022

*J Fluoresc*
<https://doi.org/10.1007/s10895-022-02961-y>

*Chlamydia trachomatis* (*C. trachomatis*) is a kind of intracellular parasitic microorganism, which can cause many diseases such as trachoma. In this strategy, a specific hairpin DNA with the probe loop as specific regions to recognize *C. trachomatis* DNA with strong affinity was designed, and its stem consisted of 24 AT base pairs as an effective template for hairpin DNA-CuNCs formation. In the absence of *C. trachomatis* DNA, the detection system showed strong orange fluorescence emission peaks at 606 nm. In the presence of *C. trachomatis* DNA, the conformation of DNA probe changed after hybridizing with *C. trachomatis* DNA. Then, the amount of hairpin DNA-CuNCs was reduced and resulted in low fluorescence emission. *C. trachomatis* DNA displayed a significant inhibitory effect on the synthesis of fluorescent hairpin DNA-CuNCs due to the competition between *C. trachomatis* DNA and the specific hairpin DNA. Under the optimal experimental conditions, different concentrations of *C. trachomatis* were tested and the results showed a good linear relationship in the range of 50 nM to 950 nM. Moreover, the detection limit was 18.5 nM and this detection method possessed good selectivity. Finally, the fluorescent biosensor had been successfully applied to the detection of *C. trachomatis* target sequence in HeLa cell lysate, providing a new strategy for the detection of *C. trachomatis*.

### Expression and structure of the *Chlamydia trachomatis* DksA ortholog.

**Mandel, C., Yang, H., Buchko, G., Abendroth, J., Grieshaber, N., Chiarelli, T., Grieshaber, S., Omsland, A.**

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*Pathog Dis*

<https://pubmed.ncbi.nlm.nih.gov/35388904>

*Chlamydia trachomatis* is a bacterial obligate intracellular parasite and a significant cause of human disease, including sexually transmitted infections and trachoma. The bacterial RNA polymerase-binding protein DksA is a transcription factor integral to the multicomponent bacterial stress response pathway known as the stringent response. The genome of *C. trachomatis* encodes a DksA ortholog (DksACT) that is maximally expressed at 15-20 h post infection, a time frame correlating with the onset of transition between the replicative reticulate body (RB) and infectious elementary body (EB) forms of the pathogen. Ectopic overexpression of DksACT in *C. trachomatis* prior to RB-EB transitions during infection of HeLa cells resulted in a 39.3% reduction in overall replication (yield) and a 49.6% reduction in recovered EBs. While the overall domain organization of DksACT is similar to the DksA ortholog of *Escherichia coli* (DksAEC), DksACT did not functionally complement DksAEC. Transcription of dksACT is regulated by tandem promoters, one of which also controls expression of *nrdR*, encoding a negative regulator of deoxyribonucleotide biosynthesis. The phenotype resulting from ectopic expression of DksACT and the correlation between dksACT and *nrdR* expression is consistent with a role for DksACT in the *C. trachomatis* developmental cycle.

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## ULCERE DE BURULI

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### PIAN

#### **Yaws elimination in Ecuador: Findings of a serological survey of children in Esmeraldas province to evaluate interruption of transmission.**

**Cooper, P., Anselmi, M., Caicedo, C., Lopez, A., Vicuña, Y., Cagua Ordoñez, J., Rivera Bonilla, J., Rodriguez, A., Soto, A., Guevara, A.**

25-05-2022

*PLoS Negl Trop Dis*

<https://doi.org/10.1371/journal.pntd.0010173>

**Background:** The WHO roadmap for neglected tropical diseases includes yaws eradication requiring certification of elimination of transmission in all endemic and formerly endemic countries worldwide. A community-based programme for yaws control was considered to have achieved elimination of the infection in the endemic focus in Ecuador after 1993. We did a serosurvey of children in this focus to provide evidence for interruption of transmission. **Methods:** Survey of serum samples collected from children aged 2 to 15 years living in the formerly endemic and in geographically contiguous areas. A convenience sample of sera collected between 2005 and 2017 from non-yaws studies, were

analyzed using immunochromatic rapid tests to screen (OnSite Syphilis Ab Combo Rapid Test) for *Treponema pallidum*-specific antibodies and confirm (DPP Syphilis Screen and Confirm) seroreactivity based on the presence antibodies to treponemal and non-treponemal antigens. **Results:** Seroreactivity was confirmed in 6 (0.14%, 95% CI 0.06-0.30) of 4,432 sera analyzed and was similar in formerly endemic (0.11%, (95% CI 0.01-0.75) and non-endemic (0.14%, 95% CI 0.06-0.34) communities. All seroreactors were of Afro-Ecuadorian ethnicity and most were male (4/6) and aged 10 or more years (5/6), the latter possibly indicating venereal syphilis. Only 1 seroreactor lived in a community in the Rio Santiago, that was formerly hyperendemic for yaws. **Conclusion:** We observed very low levels of treponemal transmission in both formerly endemic and non-endemic communities which might be indicative of congenital or venereal syphilis and, if yaws, would likely be insufficient to maintain transmission of this endemic childhood infection. Additional surveys of children aged 1 to 5 years are planned in Rio Santiago communities to exclude yaws transmission.

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## LEPRE

#### **Canine leproid granuloma (CLG) caused by mycobacterial species closely related to members of *Mycobacterium simiae* complex in a dog in Brazil.**

**Bieuz, G., de Cristo, T., Ikuta, C., Carniel, F., Volpato, J., Teixeira, M., Neto, J., Casagrande, R.**

26-05-2022

*Top Companion Anim Med*

<https://pubmed.ncbi.nlm.nih.gov/35644473>

This report describes the clinical features and molecular diagnosis of a case of canine leproid granuloma (CLG) caused by mycobacterial strains of the *Mycobacterium simiae* complex in Brazil. A 12-year-old non-neutered male Labrador Retriever dog was presented with a two-week history of progressive painless cutaneous lesions. Ulcerated nodules with hematic crusts were observed on the dorsal surface of the right and left pinna and on the metacarpal, metatarsal, and digits. Complete blood count, serum biochemistry, aspiration cytology of cutaneous lesions, biopsy for histopathological evaluation, culture for aerobic and anaerobic bacteria, polymerase chain reaction (PCR) and DNA sequencing to identify mycobacterial species were performed. According to the clinical and histopathological findings, a diagnosis of CLG was established. Despite the negative result of the bacterial culture, mycobacterial identification was made by sequencing the *hsp65* gene. Our findings highlight that mycobacterial species closely related to members of the *M. simiae* clade can be causative agents of CLG.

### Risk factors for Dapsone Resistance in Leprosy Patients: A systematic meta-analysis.

Wu, Z., Wang, C., Wang, Z., Shi, Y., Jiang, H., Wang, H.  
25-05-2022

*J Glob Antimicrob Resist*

<https://pubmed.ncbi.nlm.nih.gov/35643395>

**Objective:** Dapsone is one of the important drugs in the treatment of leprosy. The present study aims to evaluate the resistance of *Mycobacterium leprae* isolates to dapsone, in turn assisting in implement better control strategies for leprosy elimination. **Methods:** A systematic literature search was conducted in PubMed, Embase, Medline and Web of Science. Two independent reviewers selected the literature according to PRISMA guidelines, extracted data, and evaluated the risk of bias. Drug resistance data was pooled using the random effect model. Subgroup analysis was performed based on across sampling time, region, study population (treatment status, relapses status), and sample size. **Results:** A total of 30 studies were included. The results of meta-analysis showed that the dapsone resistance rate of leprosy patients after treatment was 8% [95% CI, 6% to 10%]. Compared to the rates of primary resistance of new cases without treatment therapy (pooled incidence, 4% [95% CI, 2% to 5%]), treatment cases (13% [95% CI 9% to 16%]) had secondary resistance, and relapse cases (26% [95% CI, 18% to 33%]) had drug resistance. In addition, the drug resistance rate of monotherapy was significantly increased than that of relapsed patients treated with diamino-diphenylsulfone monotherapy. Subgroup analysis showed that the patients in Western Pacific has the highest dapsone resistance and the resistance to dapsone was slightly lower after 2005. For sample size, the rate in the group under 100 samples were significantly higher than in the other. **Conclusion:** Dapsone resistance is closely related to leprosy relapse and long-term drug use. Dapsone monotherapy is one of important reason for drug resistance in relapsed cases. Differences in drug resistance in different populations and different regions of the world.

### *Caralluma edulis* (Apocynaceae): A comprehensive review on its Traditional uses, Phytochemical profile and pharmacological effects.

Ansari, B., Behl, T., Pirzada, A., Khan, H.  
27-05-2022

*Curr Top Med Chem*

<https://doi.org/10.2174/1568026622666220527092825>

*Caralluma edulis* is a well-known species of the genus *Caralluma* from Apocynaceae, commonly known as chunga. *Caralluma* species are mostly succulent perennial herbs, several of which are edible species. The plant has an outstanding therapeutic background in the traditional system of treatment. It has been recommended for the treatment of a number medical disorder such as hypertension, Alzheimer disease, rheumatism, gastric problems and leprosy. Traditionally the stem was boiled in water and this extract was then used to cure diabetes. The pharmacological effects of *C.edulis* have also been explored in various in vitro and in vivo

experiments. In this regard, the extract of the plant exhibited strong antioxidant activity, analgesic, against inflammation as well as xylene mediated ear edema for topical effects. The significant anti-hyperlipidemic effect of the plant extract is also reported. However, the extract was found insignificant in the reversal of alloxan-induced diabetes in rabbit model at test doses. These pharmacological effects are strongly supported by the presence of different bioactive phytochemicals in the plant. These groups of compounds include sterols, terpenoids, flavonoids, and pregnane glycosides. *C.edulis* is a very potential member of the genus *Caralluma* with strong traditional history, phytochemistry and phytopharmacology, needed further exploration for clinically used lead compounds. In this review, we have focused to combined different reported data on the traditional uses of the plant, phytochemical profile and pharmacological effects in different experimental assay and subsequent future prospects.

### Painful bullae in a febrile woman: a clue to first presentation of multibacillary Hansen's disease.

Laishram, R., Sophia, M., Hazarika, N.

26-05-2022

*BMJ Case Rep*

<https://pubmed.ncbi.nlm.nih.gov/35618339>

### Primary neural leprosy: clinical, neurophysiological and pathological presentation and progression.

Tomaselli, P., Dos Santos, D., Dos Santos, A., Antunes, D., Marques, V., Foss, N., Moreira, C., Nogueira, P., Nascimento, O., Neder, L., Barreira, A., Frade, M., Goulart, I., Marques, W.

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*Brain*

<https://doi.org/10.1093/brain/awab396>

Disability in leprosy is a direct consequence of damage to the peripheral nervous system which is usually worse in patients with no skin manifestations, an underdiagnosed subtype of leprosy known as primary neural leprosy. We evaluated clinical, neurophysiological and laboratory findings of 164 patients with definite and probable primary neural leprosy diagnoses. To better understand the disease progression and to improve primary neural leprosy clinical recognition we compared the characteristics of patients with short ( $\leq 12$  months) and long ( $> 12$  months) disease duration. Positive and negative symptoms mediated by small-fibres were frequent at presentation ( $\sim 95\%$ ), and symptoms tend to manifest first in the upper limbs ( $\sim 68\%$ ). There is a consistent phenotypic variability between the aforementioned groups. Deep sensory modalities were spared in patients evaluated within the first 12 months of the disease, and were only affected in patients with longer disease duration ( $\sim 12\%$ ). Deep tendon reflexes abnormalities were most frequent in patients with longer disease duration ( $P < 0.001$ ), as well as motor deficits ( $P = 0.002$ ). Damage to large fibres (sensory and motor) is a latter event in primary neural leprosy. Grade-2 disability and nerve thickening was also more frequent in cases with long disease

duration ( $P < 0.001$ ). Primary neural leprosy progresses over time and there is a marked difference in clinical phenotype between patients with short and long disease duration. Patients assessed within the first 12 months of symptom onset had a non-length-dependent predominant small-fibre sensory neuropathy, whilst patients with chronic disease presented an asymmetrical all diameter sensory-motor neuropathy and patchily decreased/absent deep tendon reflexes.

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## TRYPANOSOMES (TRYPANOSOMIASE ET MALADIE DE CHAGAS)

### **Automatic detection of the parasite *Trypanosoma cruzi* in blood smears using a machine learning approach applied to mobile phone images.**

**Morais, M., Silva, D., Milagre, M., de Oliveira, M., Pereira, T., Silva, J., Costa, L., Minoprio, P., Junior, R., Gazzinelli, R., de Lana, M., Nakaya, H.**

27-05-2022

PeerJ

<https://doi.org/10.7717/peerj.13470>

Chagas disease is a life-threatening illness caused by the parasite *Trypanosoma cruzi*. The diagnosis of the acute form of the disease is performed by trained microscopists who detect parasites in blood smear samples. Since this method requires a dedicated high-resolution camera system attached to the microscope, the diagnostic method is more expensive and often prohibitive for low-income settings. Here, we present a machine learning approach based on a random forest (RF) algorithm for the detection and counting of *T. cruzi* trypomastigotes in mobile phone images. We analyzed micrographs of blood smear samples that were acquired using a mobile device camera capable of capturing images in a resolution of 12 megapixels. We extracted a set of features that describe morphometric parameters (geometry and curvature), as well as color, and texture measurements of 1,314 parasites. The features were divided into train and test sets (4:1) and classified using the RF algorithm. The values of precision, sensitivity, and area under the receiver operating characteristic (ROC) curve of the proposed method were 87.6%, 90.5%, and 0.942, respectively. Automating image analysis acquired with a mobile device is a viable alternative for reducing costs and gaining efficiency in the use of the optical microscope.

### **Chagas disease (American trypanosomiasis) in the context of the 2030 agenda. Insights into global warming and vector control.**

**Jurberg, J.**

27-05-2022

Mem Inst Oswaldo Cruz

<https://pubmed.ncbi.nlm.nih.gov/35649050>

### **How is global change affecting Chagas disease landscapes?**

**Gürtler, R.**

27-05-2022

Mem Inst Oswaldo Cruz

<https://pubmed.ncbi.nlm.nih.gov/35649049>

### **Chagas disease in the context of the 2030 agenda: global warming and vectors.**

**Souza, R., Gorla, D., Chame, M., Jaramillo, N., Monroy, C., Diotaiuti, L.**

27-05-2022

Mem Inst Oswaldo Cruz

<https://pubmed.ncbi.nlm.nih.gov/35649048>

The 2030 Agenda for Sustainable Development is a plan of action for people, planet and prosperity. Thousands of years and centuries of colonisation have passed the precarious housing conditions, food insecurity, lack of sanitation, the limitation of surveillance, health care programs and climate change. Chagas disease continues to be a public health problem. The control programs have been successful in many countries in reducing transmission by *T. cruzi*; but the results have been variable. WHO makes recommendations for prevention and control with the aim of eliminating Chagas disease as a public health problem. Climate change, deforestation, migration, urbanisation, sylvatic vectors and oral transmission require integrating the economic, social, and environmental dimensions of sustainable development, as well as the links within and between objectives and sectors. While the environment scenarios change around the world, native vector species pose a significant public health threat. The man-made atmosphere change is related to the increase of triatomines' dispersal range, or an increase of the mobility of the vectors from their sylvatic environment to man-made constructions, or humans getting into sylvatic scenarios, leading to an increase of Chagas disease infection. Innovations with the communities and collaborations among municipalities, International cooperation agencies, local governmental agencies, academic partners, developmental agencies, or environmental institutions may present promising solutions, but sustained partnerships, long-term commitment, and strong regional leadership are required. A new world has just opened up for the renewal of surveillance practices, but the lessons learned in the past should be the basis for solutions in the future.

### **Early identification of patients with Chagas disease at risk of developing cardiomyopathy using 2-D speckle tracking strain: Win, Miranda prediction of Chagas cardiomyopathy.**

**Win, S., Miranda-Schaeubinger, M., Gustavo Durán Saucedo, R., Carballo Jimenez, P., Flores, J., Mercado-Saavedra, B., Camila Telleria, L., Raafs, A., Verastegui, M., Bern, C., Tinajeros, F., Heymans, S., Marcus, R., Gilman, R., Mukherjee, M., Chagas Working Group**

23-05-2022

Int J Cardiol Heart Vasc

<https://doi.org/10.1016/j.ijcha.2022.101060>

**Background:** Chagas disease is an endemic protozoan disease with high prevalence in Latin America. Of those infected, 20-30% will develop chronic Chagas cardiomyopathy (CCC) however, prediction using existing clinical criteria remains poor. In this study, we investigated the utility of left ventricular (LV) echocardiographic speckle-tracking global longitudinal strain (GLS) for early detection of CCC. **Methods and results:** 139 asymptomatic *T. cruzi* seropositive subjects with normal heart size and normal LV ejection fraction (EF) (stage A or B) were enrolled in this prospective observational study and underwent paired echocardiograms at baseline and 1-year follow-up. Progressors were participants classified as stage C or D at follow-up due to development of symptoms of heart failure, cardiomegaly, or decrease in LVEF. LV GLS was calculated as the average peak systolic strain of 16 LV segments. Measurements were compared between participants who progressed and did not progress by two-sample *t*-test, and the odds of progression assessed by multivariable logistic regression. Of the 139 participants, 69.8% were female, mean age  $55.8 \pm 12.5$  years, with 12 (8.6%) progressing to Stage C or D at follow-up. Progressors tended to be older, male, with wider QRS duration. LV GLS was  $-19.0\%$  in progressors vs.  $-22.4\%$  in non-progressors at baseline, with 71% higher odds of progression per +1% of GLS (adjusted OR 1.71, 95% CI 1.20-2.44,  $p = 0.003$ ). **Conclusion:** Baseline LV GLS in participants with CCC stage A or B was predictive of progression within 1-year and may guide timing of clinical follow-up and promote early detection or treatment.

### Cost-effectiveness of an Exercise-Based Cardiovascular Rehabilitation Program in Patients with Chronic Chagas Cardiomyopathy in Brazil: an analysis from the PEACH Study.

Simões, V., Mendes, F., Avellar, A., da Silva, G., Carneiro, F., da Silva, P., Mazzoli-Rocha, F., Silva, R., Vieira, M., do Nascimento Costa, C., de Sousa, A., Rosalino, C., da Silva Nobre, P., de Holanda, M., Costa, H., Saraiva, R., Hasslocher-Moreno, A., Castro, R., Mediano, M.

29-05-2022

Trop Med Int Health

<https://doi.org/10.1111/tmi.13784>

**Objectives:** The present study aimed to perform a cost-effectiveness analysis of an exercise-based cardiovascular rehabilitation (CR) program in patients with chronic Chagas cardiomyopathy (CCC). **Methods:** Cost-effectiveness analysis alongside a randomized clinical trial evaluating the effects of a 6-month exercise-based CR program. The intervention group underwent three weekly exercise sessions. The variation of peak oxygen consumption ( $VO_{2peak}$ ) was used as a measurement of clinical outcome. Cost information from all healthcare expenses (examinations, healthcare visits, medication, and hospitalization) were obtained from the medical records in Brazilian reais (R\$) and transformed into

dollars using the purchasing power parity (\$PPP). The longitudinal costs variation was evaluated through linear mixed models, represented by  $\beta$  coefficient, adjusted for the baseline values of the dependent variable. The cost-effectiveness evaluation was determined through an incremental cost-effectiveness ratio using the HEABS package (Stata 15.0). **Results:** The intervention group presented higher costs with healthcare visits ( $\beta = +3,317.3$ ;  $p < 0.001$ ), hospitalization ( $\beta = +2,810.4$ ;  $p = 0.02$ ) and total cost ( $\beta = +6,407.9$ ;  $p < 0.001$ ) after three months of follow-up. Costs related to healthcare visits ( $\beta = +2,455.8$ ;  $p < 0.001$ ) and total cost ( $\beta = +4,711.4$ ;  $p < 0.001$ ) remained higher in the intervention group after six months. The CR program showed an incremental cost-effectiveness ratio (ICER) of \$PPP 1,874.3 for each increase of  $1.0 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  of  $VO_{2peak}$ . **Conclusions:** The CR program can be considered a cost-effective alternative and should be included as an intervention strategy in the care of patients with CCC.

### Do not judge a book by its cover: would *Triatoma tibiamaculata* (Pinto, 1926) belong to *Triatoma Laporte, 1832*, or to *Panstrongylus Berg, 1879*, with misleading homoplasies?

Bittinelli, I., de Oliveira, J., Dos Reis, Y., Ravazi, A., Madeira, F., de Oliveira, A., Montanari, G., Gomes, A., Cesaretto, L., Massarin, I., Galvão, C., de Azevedo-Oliveira, M., da Rosa, J., Alevi, K.

28-05-2022

Parasit Vectors

<https://doi.org/10.1186/s13071-022-05314-7>

**Background:** *Triatoma tibiamaculata* is a species distributed in ten Brazilian states which has epidemiological importance as it has already been found infecting household areas. The taxonomy of this triatomine has been quite unstable: it was initially described as *Eutriatoma tibiamaculata*. Later, the species was transferred from the genus *Eutriatoma* to *Triatoma*. Although included in the genus *Triatoma*, the phylogenetic position of *T. tibiamaculata* in relation to other species of this genus has always been uncertain once this triatomine was grouped in all phylogenies with the genus *Panstrongylus*, rescuing *T. tibiamaculata* and *P. megistus* as sister species. Thus, we evaluated the generic status of *T. tibiamaculata* using phylogenetic and chromosomal analysis. **Methods:** Chromosomal (karyotype) and phylogenetic (with mitochondrial and nuclear markers) analyses were performed to assess the relationship between *T. tibiamaculata* and *Panstrongylus* spp. **Results:** The chromosomal and phylogenetic relationship of *T. tibiamaculata* and *Panstrongylus* spp. confirms the transfer of the species to *Panstrongylus* with the new combination: *Panstrongylus tibiamaculatus*. **Conclusions:** Based on chromosomal and phylogenetic characteristics, we state that *P. tibiamaculatus* comb. nov. belongs to the genus *Panstrongylus* and that the morphological features shared with *Triatoma* spp. represent homoplasies.

### An updated catalog of lipocalins of the chagas disease vector *Rhodnius prolixus* (Hemiptera, Reduviidae).

Santos, D., Gontijo, N., Pessoa, G., Sant'Anna, M., Araujo, R., Pereira, M., Koerich, L.

28-05-2022

*Insect Biochem Mol Biol*

<https://pubmed.ncbi.nlm.nih.gov/35640811>

The haematophagy process by arthropods has been one of the main targets of studies in the parasite-host interaction, and the kissing-bug *Rhodnius prolixus*, vector of the protozoan *Trypanosoma cruzi*, has been one of the main models for such studies. Still in the 1980s, it was identified that among the salivary proteins for disrupting vertebrate host homeostasis, lipocalins were among the most relevant proteins for this process. Since then, 30 lipocalins have been identified in the salivary glands of *R. prolixus*, that promotes vasodilatation, prevents inflammation, act as anticoagulants and inhibits platelet aggregation. The present work aims to identify new lipocalins from *R. prolixus*, combining transcriptome and genome data. Identified new genes were mapped and had their structure annotated. To infer an evolutionary relationship between lipocalins, and to support the predicted functions for each lipocalin, all amino acid sequences were used to construct phylogenetic trees. We identified a total of 29 new lipocalins, 3 new bioaminogenic-binding proteins (which act to inhibit platelet aggregation and vasodilatation), 9 new inhibitors of platelet aggregation, 7 new apolipoproteins and 10 lipocalins with no putative function. In addition, we observed that several of the lipocalins are also expressed in different *R. prolixus* tissues, including gut, central nervous system, antennae, and reproductive organs. In addition to newly identified lipocalins and a mapping the new and old lipocalins in the genome of *R. prolixus*, our study also carried out a review on functional status and nomenclature of some of the already identified lipocalins. Our study reinforces that we are far from understanding the role of lipocalins in the physiology of *R. prolixus*, and that studies of this family are still of great relevance.

### Prevalence and animal level risk factors associated with *Trypanosoma evansi* infection in dromedary camels.

Selim, A., Alafari, H., Attia, K., AlKahtani, M., Albohairy, F., Elsohaby, I.

27-05-2022

*Sci Rep*

<https://doi.org/10.1038/s41598-022-12817-x>

Surra is a non-cyclic parasitic disease caused by *Trypanosoma evansi* (*T. evansi*) and spread by biting flies. The disease has a severe impact on camel health, productivity, and market value, posing a significant threat to food safety and the economy. In a cross-sectional study, 370 blood samples were collected from camels in three Egyptian governorates. Samples were tested using parasitological (thin blood smear (TBS)), card agglutination test for *T. evansi* (CATT), and PCR to

estimate the prevalence of *T. evansi* infection. Overall, the prevalence of *T. evansi* among examined camels was 17.3%, 18.9% and 22.7% using TBS, CATT and PCR methods, respectively. The risk of *T. evansi* infection in older camels (>10 years) is higher than that in young ones (odds ratio (OR)=9; 95% CI: 3.5-23.1), particularly during spring (OR=2.5; 95% CI: 1.1-5.7). Furthermore, females and poor conditioned camels were 2.6 and four times more likely to get infection than males and good conditioned camels, respectively. The level of agreement between diagnostics tests were perfect kappa (>0.83). Moreover, CATT showed higher sensitivity (0.83; 95% CI: 0.74-0.91) than TBS (0.76; 95% CI: 0.66-0.85) and both had perfect specificity (100%). In conclusion, our findings revealed a high rate of *T. evansi* infection in camels from the three Egyptian governorates. The CATT is a good test for routine use in control program of trypanosomiasis in camels.

### Chagas Disease in Oklahoma.

Revue de littérature

Higueta, N., Bronze, M., Smith, J., Montgomery, S.

24-05-2022

*Am J Med Sci*

<https://pubmed.ncbi.nlm.nih.gov/35623395>

Chagas disease, caused by infection with the protozoan *Trypanosoma cruzi*, is one of the leading public health problems in the Western Hemisphere. The parasite is mainly transmitted by contact with infected insect vectors but other forms of transmission are important in endemic areas. In the United States, while the disease is largely restricted to immigrants from endemic countries in Latin America, there is some risk of local acquisition. *T. cruzi* circulates in a sylvatic cycle between mammals and local triatomine insects in the southern half of the country, where human residents may be at risk for incidental infection. There are several reported cases of locally-acquired Chagas disease in the United States, but there is a paucity of information in Oklahoma. We present a brief summary of the available data of Chagas disease in Oklahoma to raise awareness and serve as a foundation for future research.

### Structure, function and druggability of the African trypanosome flagellum.

Revue de littérature

Sáez Conde, J., Dean, S.

26-05-2022

*J Cell Physiol*

<https://doi.org/10.1002/jcp.30778>

African trypanosomes are early branching protists that cause human and animal diseases, termed trypanosomiases. They have been under intensive study for more than 100 years and have contributed significantly to our understanding of eukaryotic biology. The combination of conserved and parasite-specific features mean that their flagellum has gained particular attention. Here, we discuss the different structural

features of the flagellum and their role in transmission and virulence. We highlight the possibilities of targeting flagellar function to cure trypanosome infections and help in the fight to eliminate trypanosomiases.

### **Chagas disease treatment: a 120-year-old challenge to public health.**

**Goldenberg, S.**

23-05-2022

*Mem Inst Oswaldo Cruz*

<https://pubmed.ncbi.nlm.nih.gov/35613159>

### **Revisiting Chagas' disease diagnostic strategies in light of different scenarios of *Trypanosoma cruzi* infection.**

**Britto, C.**

23-05-2022

*Mem Inst Oswaldo Cruz*

<https://pubmed.ncbi.nlm.nih.gov/35613158>

### **Air in the tires: towards an achievable, efficacious and timely diagnosis for Chagas disease.**

**Angheben, A.**

23-05-2022

*Mem Inst Oswaldo Cruz*

<https://pubmed.ncbi.nlm.nih.gov/35613157>

### **The translational challenge in Chagas disease drug development.**

Revue de littérature

**Kratz, J., Gonçalves, K., Romera, L., Moraes, C., Bittencourt-Cunha, P., Schenkman, S., Chatelain, E., Sosa-Estani, S.**

23-05-2022

*Mem Inst Oswaldo Cruz*

<https://pubmed.ncbi.nlm.nih.gov/35613156>

Chagas disease is a neglected tropical disease caused by the protozoan parasite *Trypanosoma cruzi*. There is an urgent need for safe, effective, and accessible new treatments since the currently approved drugs have serious limitations. Drug development for Chagas disease has historically been hampered by the complexity of the disease, critical knowledge gaps, and lack of coordinated R&D efforts. This review covers some of the translational challenges associated with the progression of new chemical entities from preclinical to clinical phases of development, and discusses how recent technological advances might allow the research community to answer key questions relevant to the disease and to overcome hurdles in R&D for Chagas disease.

### **Parasitological, serological and molecular diagnosis of acute and chronic Chagas disease: from field to laboratory.**

**Schijman, A., Alonso-Padilla, J., Longhi, S., Picado, A.**

23-05-2022

*Mem Inst Oswaldo Cruz*

<https://pubmed.ncbi.nlm.nih.gov/35613155>

There is no consensus on the diagnostic algorithms for many scenarios of *Trypanosoma cruzi* infection, which hinders the establishment of governmental guidelines in endemic and non-endemic countries. In the acute phase, parasitological methods are currently employed, and standardised surrogate molecular tests are being introduced to provide higher sensitivity and less operator-dependence. In the chronic phase, IgG-based serological assays are currently used, but if a single assay does not reach the required accuracy, PAHO/WHO recommends at least two immunological tests with different technical principles. Specific algorithms are applied to diagnose congenital infection, screen blood and organ donors or conduct epidemiological surveys. Detecting Chagas disease reactivation in immunosuppressed individuals is an area of increasing interest. Due to its neglect, enhancing access to diagnosis of patients at risk of suffering *T. cruzi* infection should be a priority at national and regional levels.

### **Antiparasitary and antiproliferative activities in vitro of a 1,2,4-oxadiazole derivative on *Trypanosoma cruzi*.**

**Rocha, Y., Magalhães, E., de Medeiros Chaves, M., Machado Marinho, M., Nascimento E Melo de Oliveira, V., Nascimento de Oliveira, R., Lima Sampaio, T., de Menezes, R., Martins, A., Nicolete, R.**

25-05-2022

*Parasitol Res*

<https://doi.org/10.1007/s00436-022-07554-z>

Chagas disease (CD) is a neglected disease, prevalent and endemic in Latin America, but also present in Europe and North America. The main treatment used for this disease is benznidazole, but its efficacy is variable in the chronic phase and presents high toxicity. So, there is a need for the development of new therapeutic agents. The five-membered heterocyclic 1,2,4-oxadiazole ring has received attention for its unique properties and a broad spectrum of biological activities and is therefore a potential candidate for the development of new drugs. Thus, the aim of this study was to evaluate the activity of the N-cyclohexyl-3-(3-methylphenyl)-1,2,4-oxadiazol-5-amine (2) on the evolutionary forms of *Trypanosoma cruzi* strain Y, as well as its mechanisms of action and in silico theoretical approach. The results by computational method showed an interaction of the 1,2,4-oxadiazole (2) with TcGAPDH, cruzain, and trypanothione reductase, showing good charge distribution and affinity in those three targets. Furthermore, cytotoxicity in LLC-MK<sub>2</sub> cells was performed by the MTT method. In the assays with different parasite forms, the tested compound showed similar time-dependent concentration effect. The evaluation of the anti-amastigote effect between the two concentrations tested showed a reduction in the number of infected cells and also in the number of amastigotes per infected cell. By flow cytometry, the compound (2) displayed alterations suggestive

of necrotic events. Finally, in scanning electron microscopy structural alterations were present, characteristic of necrosis in the epimastigote forms. Overall, the 1,2,4-oxadiazole derivative (2) here evaluated opens perspectives to the development of new antichagasic agents.

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

Van Den Broucke, S., Van Herreweghe, M., Breynaert, A., Van Esbroeck, M., Truyens, C., De Bruyne, T., Hermans, N., Huits, R.

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*J Antimicrob Chemother*

<https://doi.org/10.1093/jac/dkac093>

**Background:** Benznidazole is an effective drug in the trypanocidal treatment of acute and chronic indeterminate Chagas' disease (CD). However, adverse drug reactions (ADR) are common and frequently cause patients to discontinue treatment. **Objectives:** We hypothesized that antioxidant supplementation could mitigate benznidazole-induced toxicity. **Methods:** We co-supplemented an adult traveller with chronic indeterminate CD who experienced benznidazole ADR with ascorbic acid (AA), 1000 mg/day. We measured selected serum biomarkers of oxidative stress [total antioxidant status (TAS), total oxidative status (TOS), nuclear factor erythroid 2-related factor 2 (Nrf2), malondialdehyde (MDA), extracellular glutathione peroxidase (GPX3), catalase (CAT) and total superoxide dismutase (T-SOD)] at timepoints before and throughout benznidazole treatment and after AA co-supplementation. **Results:** AA co-supplementation effectively mitigated benznidazole-induced ADR during the aetiological treatment of chronic indeterminate CD. The kinetics of serum biomarkers of oxidative stress suggested significantly decreased oxidative insult in our patient. **Conclusions:** We hypothesize that the key pathophysiological mechanism of benznidazole-associated toxicity is oxidative stress, rather than hypersensitivity. AA co-supplementation may improve adherence to benznidazole treatment of chronic indeterminate (or acute) CD. Oxidative stress biomarkers have the potential to guide the clinical management of CD. Prospective studies are needed to establish the benefit of antioxidant co-supplementation to benznidazole treatment of CD in reducing benznidazole toxicity, parasite clearance and the prevention of end-organ damage.

### Fragment-Based Drug Discovery for *Trypanosoma brucei* Glycosylphosphatidylinositol-Specific Phospholipase C through Biochemical and WaterLOGSY-NMR Methods.

Ibrahim, M., Yamasaki, T., Furukawa, K., Yamasaki, K.

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*J Biochem*

<https://doi.org/10.1093/jb/mvac020>

Glycosylphosphatidylinositol-specific phospholipase C (GPI-

PLC) of *Trypanosoma brucei*, the causative protozoan parasite of African trypanosomiasis, is a membrane-bound enzyme essential for antigenic variation, because it catalyses the release of the membrane-bound form of variable surface glycoproteins. Here, we performed a fragment-based drug discovery of TbGPI-PLC inhibitors using a combination of enzymatic inhibition assay and water ligand observed via gradient spectroscopy (WaterLOGSY) NMR experiment. The TbGPI-PLC was cloned and overexpressed using an *Escherichia coli* expression system followed by purification using three-phase partitioning and gel filtration. Subsequently, the inhibitory activity of 873 fragment compounds against the recombinant TbGPI-PLC led to the identification of 66 primary hits. These primary hits were subjected to the WaterLOGSY NMR experiment where 10 fragment hits were confirmed to directly bind to the TbGPI-PLC. These included benzothiazole, chlorobenzene, imidazole, indole, pyrazol and quinolinone derivatives. Molecular docking simulation indicated that six of them share a common binding site, which corresponds to the catalytic pocket. The present study identified chemically diverse fragment hits that could directly bind and inhibit the TbGPI-PLC activity, which constructed a framework for fragment optimization or linking towards the design of novel drugs for African trypanosomiasis.

## LEISHMANIOSE

### Ivermectin and curcumin cause plasma membrane rigidity in *Leishmania amazonensis* due to oxidative stress.

Alonso, L., Dorta, M., Alonso, A.

30-05-2022

*Biochim Biophys Acta Biomembr*

<https://pubmed.ncbi.nlm.nih.gov/35654148>

Spin label electron paramagnetic resonance (EPR) spectroscopy was used to study the mechanisms of action of ivermectin and curcumin against *Leishmania (L.) amazonensis* promastigotes. EPR spectra showed that treatment of the parasites with both compounds results in plasma membrane rigidity due to oxidative processes. With the IC<sub>50</sub> and EPR measurements for assays using different parasite concentrations, estimations could be made for the membrane-water partition coefficient (K<sub>M/W</sub>), and the concentration of the compound in the membrane (c<sub>m50</sub>) and in the aqueous phase (c<sub>w50</sub>), which inhibits cell growth by 50%. The K<sub>M/W</sub> values indicated that ivermectin has a greater affinity than curcumin for the parasite membrane. Therefore, the activity of ivermectin was higher for experiments with low cell concentrations, but for concentrations greater than 1.5 × 10<sup>8</sup> parasites/mL the compounds did not show significantly different results. The c<sub>m50</sub> values indicated that the concentration of compound in the membrane leading to growth inhibition or membrane alteration is approximately

1 M for both ivermectin and curcumin. This high membrane concentration suggests that many ivermectin molecules per chlorine channel are needed to cause an increase in chlorine ion influx.

### Report of autochthonous cases of localized cutaneous leishmaniasis caused by *Leishmania (Leishmania) mexicana* in vulnerable, susceptible areas of Southeastern Mexico.

**Canché-Pool, E., Canto-Hau, D., Vargas-Meléndez, M., Tello-Martín, R., Reyes-Novelo, E., Escobedo-Ortegón, F., Ruiz-Piña, H., Cambranes-Puc, L., Torres-Castro, J., Palacio-Vargas, J., Durán-Caamal, C., Cerón-Espinosa, J., Carpio-Pedroza, J., Rivera-Hernández, O.**  
25-05-2022

*Rev Inst Med Trop Sao Paulo*

<https://pubmed.ncbi.nlm.nih.gov/35648988>

Localized cutaneous leishmaniasis (LCL) is an endemic disease in several Mexican States with the main endemic areas located in the South-Southeast region of the country, where 90% of *Leishmania (Leishmania) mexicana* cases are registered. The Southeast region is located in the Yucatan Peninsula, including Campeche, Quintana Roo and Yucatan States. Campeche and Quintana Roo register more than 60% of the cases in the country each year, while in Yucatan the reports are of imported cases due to residents traveling to endemic areas. However, since 2015, autochthonous cases have been diagnosed by health authorities in municipalities with no previous transmission records. We aimed to identify *Leishmania* parasite species involved in autochthonous cases by means of the PCR technique. The present study included 13 autochthonous cases of LCL with clinical and parasitological diagnoses during 2018 and 2019 by health authorities, without specific identification of the causal agent. Tissue samples were taken by scraping the margins of active lesions and then they were spotted onto an FTATM Elute Microcard. Next, DNA was eluted and used for PCR amplification of specific *Leishmania* genus and *L. (L.) mexicana* species-specific fragments. Molecular analysis showed evidence that *L. (L.) mexicana* was the causal agent of LCL in 12 of the 13 patients; in one patient, PCR was not performed due to the patient's refusal to participate in the study. Identifying *Leishmania* species that cause LCL is necessary to define efficient treatment schemes and control strategies for the disease in vulnerable and susceptible areas of the Yucatan State's municipalities.

### Reprint of: Man with severe mucocutaneous leishmaniasis.

**Cárdenas, G., Travezaño, J., Chavez, M.**  
26-05-2022

*Dis Mon*

<https://pubmed.ncbi.nlm.nih.gov/35644649>

### Cutaneous leishmaniosis due to *Leishmania mexicana* in a cat treated with cryotherapy.

**Mendoza, Y., Colmenares, A., Hernández-Pereira, C., Shaban, M., Mogollón, A., Morales-Panza, R., Suarez-Alvarado, M., Sordillo, E., Kato, H., Paniz-Mondolfi, A.**  
29-05-2022

*Vet Dermatol*

<https://doi.org/10.1111/vde.13083>

We report the novel use of cryosurgery to treat cutaneous feline leishmaniosis (FeL) in a domestic cat from mid-western Venezuela. Amastigotes, evident by microscopy in aspirates from the nodular, erythematous nose lesions, were identified as *Leishmania mexicana* by cytochrome b gene sequence analysis. Lesions resolved completely without relapse after 14 months.

### Emerging computational technologies in human leishmaniasis: where are we?

**Tuon, F., Amato, V., Zequinao, T., Cruz, J.**  
30-05-2022

*Trans R Soc Trop Med Hyg*

<https://pubmed.ncbi.nlm.nih.gov/35640661>

Human leishmaniasis is a neglected tropical disease (NTD) with high morbidity and is endemic in low- to middle-income countries. Its diagnosis, treatment and epidemiological control methods are outdated and obsolete, which has become a challenge for health practitioners in controlling the disease. Computational methods have proven to be beneficial and have become popular in many fields of medicine, especially in affluent countries. However, they have not been widely used for NTDs. To date, few computational technologies have been employed for leishmaniasis. Although new technologies in leishmaniasis are theorized, they have only been minimally applied and have not been updated, even in other infections. Research and development on NTDs suffers from the inherent difficulties of the demographic regions the diseases afflict. In this narrative review we described the e-tools available in managing leishmaniasis, ranging from drug discovery to treatment.

### A "Core-Linker-Polyamine (CLP)" strategy enabling rapid discovery of antileishmanial aminoalkyl-quinoline-carboxamides that target oxidative stress mechanism.

**Shah, A., Hura, N., Babu, N., Roy, N., Rao, V., Paul, A., Roy, P., Singh, S., Guchhait, S.**  
30-05-2022

*ChemMedChem*

<https://doi.org/10.1002/cmdc.202200109>

A "Core-Linker-Polyamine (CLP)" strategy has been exploited to develop new antileishmanial agents. It involves the linker-based assembly of alkyl-polyamine side chain as a potential pharmacophore motif with a privileged heterocyclic motif, 4-arylquinoline. A series of aminoalkyl 4-arylquinoline-2-carboxamides and their analogs were synthesized and tested

against *L. donovani* promastigotes. Among all synthesized derivatives, 10 compounds showed significant antipromastigote activities with more efficacy (IC<sub>50</sub> : 4.75-8 μM) than an antileishmanial oral drug Miltefosine (IC<sub>50</sub> : 8.9±1.55 μM). Most active compounds 9a and 9b, displayed negligible cytotoxicity towards human monocytic (THP-1) macrophages. The compounds show antileishmanial activity by generating mitochondrial superoxide radicals. However, they did not show interference with trypanothione reductase, a redox enzyme of *Leishmania*. Significant change in the morphology of the *L. donovani* promastigote by the compounds was observed. The Structure-activity relationship analysis suggest the pharmacophoric importance of alkylpolyamine and carboxamide motifs. In silico evaluation indicated that the investigated active molecules 9a and 9b possess important drug-likeness, physicochemical and pharmacokinetic-relevant properties.

### Dual treatment of cutaneous leishmaniasis with topical amphotericin B and photodynamic therapy in a pediatric patient.

**Knapp, C., Vaz, L., Onoday, H., Small, A.**

30-05-2022

*Pediatr Dermatol*

<https://doi.org/10.1111/pde.15042>

Cutaneous leishmaniasis is a parasitic infection that can result in scarring, contributing to significant morbidity when a cosmetically sensitive area is involved. We report a case of a 13-year-old boy with cutaneous leishmaniasis involving the face and arm. He was treated with a combination of photodynamic therapy as well as topical amphotericin with a cosmetically satisfying outcome. This combination of noninvasive treatment regimens has not been reported to our knowledge and merits further study in the pediatric population.

### Prospects of halofuginone as an antiprotozoal drug scaffold.

Revue de littérature

**Gill, J., Sharma, A.**

27-05-2022

*Drug Discov Today*

<https://pubmed.ncbi.nlm.nih.gov/35636724>

Halofuginone is a clinically active derivative of febrifugine, first isolated from the Chinese herb *Dichroa febrifuga*. The beneficial biological effects of halofuginone on various diseases, including parasitic diseases, cancer, fibrosis, and autoimmune disorders, have been established. Halofuginone has reduced toxic side effects when compared to febrifugine, an advantage that has led to the commercial availability of halofuginone-based antiparasitic drugs and to completed early human clinical trials for the treatment of tumors and fibrosis. This review summarizes advances in determining the mechanism of action of halofuginone, focusing on its antiprotozoal role in malaria, cryptosporidiosis, coccidiosis,

toxoplasmosis, and leishmaniasis. We discuss mechanistic insights into halofuginone's primary mode of action, which involves inhibition of the prolyl-tRNA synthetase enzyme, which is crucial in protein synthesis. Halofuginone exemplifies the untapped wealth of plant-derived compounds in disease therapeutics. Teaser: Halofuginone, a plant-derived compound that acts through inhibition of the parasite prolyl-tRNA synthetase enzyme, is a promising scaffold for the design of derivatives with improved therapeutic potential as antiprotozoals.

### Fabrication and Evaluation of Voriconazole Loaded Transthesosomal Gel for Enhanced Antifungal and Antileishmanial Activity.

**Farooq, M., Usman, F., Zaib, S., Shah, H., Jamil, Q., Akbar Sheikh, F., Khan, A., Rabea, S., Hagra, S., El-Saber Batiha, G., Khan, I.**

23-05-2022

*Molecules*

<https://pubmed.ncbi.nlm.nih.gov/35630825>

Voriconazole (VRC) is a broad-spectrum antifungal agent belonging to BCS class II (biopharmaceutical classification system). Despite many efforts to enhance its solubility, this primary issue still remains challenging for formulation scientists. Transthesosomes (TEs) are one of the potential innovative nano-carriers for improving the solubility and permeation of poorly soluble and permeable drugs. We herein report voriconazole-loaded transthesosomes (VRCT) fabricated by the cold method and followed by their incorporation into carbopol 940 as a gel. The prepared VRCT were evaluated for % yield, % entrapment efficiency (EE), surface morphology, possible chemical interaction, particle size, zeta potential, and polydispersity index (PDI). The optimized formulation had a particle size of 228.2 nm, a zeta potential of -26.5 mV, and a PDI of 0.45 with enhanced % EE. Rheology, spreadability, extrudability, in vitro release, skin permeation, molecular docking, antifungal, and antileishmanial activity were also assessed for VRCT and VRC loaded transthesosomal gel (VTEG). Ex-vivo permeation using rat skin depicted a transdermal flux of 22.8 μg/cm<sup>2</sup>/h with enhanced efficiency up to 4-fold. A two-fold reduction in inhibitory as well as fungicidal concentration was observed against various fungal strains by VRCT and VTEG besides similar results against *L. donovani*. The development of transthesosomal formulation can serve as an efficient drug delivery system through a topical route with enhanced efficacy and better patient compliance.

### First Report of an Asymptomatic *Leishmania (Viannia) shawi* Infection Using a Nasal Swab in Amazon, Brazil.

**Oliveira, L., Nascimento, L., Santos, F., Takamatsu, J., Sanchez, L., Santos, W., Garcez, L.**

23-05-2022

*Int J Environ Res Public Health*

<https://pubmed.ncbi.nlm.nih.gov/35627883>

The state of Pará has recorded seven *Leishmania* species that cause tegumentary leishmaniasis (TL). *Leishmania* species induce distinct immunological responses from the host and exhibit resistance to Glucantime, the first-line drug treatment for TL in Brazil. **Objective:** Identify the etiology of TL in an Amazonian city in the state of Pará. **Material and methods:** Eleven patients with TL were recruited and nasal swabs, lesion swabs, and skin fragments samples were collected. In the control group (n = 6), only the nasal swabs were collected. Polymerase Chain Reaction (PCR) amplification of the gene region *hsp70-234* was performed using the extracted DNA from the samples, from which nine patients with TL and five in the control group were positive. Products were sequenced, mounted in CAP3 software, aligned using MAFFT v.7.221, edited in Geneious software v.8.1.7, and compared and aligned with sequences available in GenBank using the BLAST tool. **Results:** For patients with TL, six molecular diagnosis at the species level (*L. (Viannia) braziliensis* (n = 5/9), *L. (Viannia) shawi* (n = 1/9)) and three at the genus level (*Leishmania* sp. (n = 3/9)) were obtained. In the control group, four individuals were infected with *Leishmania* sp. (n = 4/5) and *L. (V.) shawi* (n = 1/5). **Conclusion:** This is the first report of *L. (V.) shawi* infection in the mucosal secretion of a healthy person in Brazil. Moreover, genetic variants were identified in the haplotypes of *L. (V.) braziliensis* in the gene sequence *hsp70-234*.

### Molecular and serological evaluation of visceral leishmaniasis in domestic dogs and cats in Maragheh County, north-west of Iran, 2018-2021.

Soleimani, A., Mohebbi, M., Gholizadeh, S., Bozorgomid, A., Shafiei, R., Raeghi, S.

27-05-2022

*Vet Med Sci*

<https://doi.org/10.1002/vms3.846>

**Objective:** Zoonotic visceral leishmaniasis (VL) is caused by *Leishmania infantum*, of which dogs are the main reservoir. VL is endemic in the Middle East, also in some parts of Iran. Following reports of new cases of VL in children in Maragheh County, the non-endemic area of the disease, we encouraged to conduct a preliminary study on domestic dogs and cats to identify their potential role as reservoirs for the disease. **Materials and methods:** This study was conducted during a period of 3 years from 2018 to 2021. Two hundred ownership dogs and 25 cats from Maragheh County, north-west of Iran, were randomly screened. Blood samples were collected. A direct agglutination test (DAT) was used for the detection of anti-*L. infantum* antibodies. Furthermore, buffy coat samples from the *L. infantum* seropositive animals were examined to detect parasite presence using polymerase chain reaction. **Results:** Out of the total of 200 ownership dogs evaluated, 170 (85%) were male and 30 (15%) were female with a mean age of 4.3 years. Anti-*L. infantum* antibodies (IgG cut-off  $\geq 1:320$ ) were observed in 3.5% of dogs (7/200) by the DAT test. All seropositive dogs were identified in the first year of examination. Regarding molecular approaches in seropositive

dogs, two samples were positive for a 565 bp kDNA minicircle gene specific for *L. infantum*. During the study period, no seropositive case was detected in the cats examined.

**Conclusions:** This study shows that the domestic cycle of *L. infantum* has been established in the studied region. It is necessary to increase the awareness and monitoring of the disease with the study of wild reservoirs periodically.

### Knowledge, attitude, and practices towards cutaneous leishmaniasis in referral cases with cutaneous lesions: A cross-sectional survey in remote districts of southern Khyber Pakhtunkhwa, Pakistan.

Ahmad, S., Obaid, M., Taimur, M., Shaheen, H., Khan, S., Niaz, S., Ali, R., Haleem, S.

26-05-2022

*PLoS One*

<https://doi.org/10.1371/journal.pone.0268801>

**Background:** Cutaneous leishmaniasis is a neglected tropical disease caused by *Leishmania* spp. and transmitted by female sandflies. Terrorism and counter-insurgency military operations in Federally Administered Tribal Areas (FATA) lead to a large-scale migration of internally displaced persons (IDPs) in Khyber Pakhtunkhwa and thus, new outbreaks of several infectious diseases such as cutaneous leishmaniasis occurred. This study intended to find the prevalence of cutaneous leishmaniasis in people with cutaneous lesions suspected of having cutaneous leishmaniasis in four remote districts of Khyber Pakhtunkhwa and to assess the participant's knowledge, attitude, and practices about the infection and its control. **Methods:** A cross-sectional study was carried out in four remote districts of Khyber Pakhtunkhwa including Karak, Lakki Marwat, Tank, and Dera Ismail Khan (D. I. Khan) and a total of 1,674 participants were recruited using a convenience sampling technique. **Results:** The prevalence of cutaneous leishmaniasis among the participants with cutaneous lesions was 50.4% and the infection was comparatively more prevalent in district Karak. Among participants, 56.8% were male and mostly, 53.8% were under the age of 16 years with 52.8% living in kutcha houses and were from rural areas. Multiple skin lesions were more common, and the face was frequently affected body part. The ratio of participants with lesions older than a month was higher and the majority confronted infections with blood protozoan parasites for the first time. Most participants were unaware of the signs/symptoms of the disease, basic knowledge of the vectors, anthroponotic spread, preventive measures, secondary infections, and reservoir hosts. The use of wood/animal dung as fuel, closeness with reservoir animals, and no use of insect repellents were some of the notable risk factors. **Conclusion:** Cutaneous leishmaniasis is highly prevalent in the study area and a very low level of awareness was reported among the participants. This study necessitates the planning and execution of regulations and preventive programs, public health education, awareness campaigns, and disease management practices to overcome future incidence of cutaneous leishmaniasis.

### The current epidemiology of leishmaniasis in Turkey, Azerbaijan and Georgia and implications for disease emergence in European countries.

Revue de littérature

Özbel, Y., Töz, S., Muñoz, C., Ortuño, M., Jumakanova, Z., Pérez-Cutillas, P., Maia, C., Conceição, C., Baneth, G., Pereira, A., Van der Stede, Y., Gossner, C., Berriatua, E.

26-05-2022

*Zoonoses Public Health*

<https://doi.org/10.1111/zph.12977>

*Leishmania* spp. are sand fly-borne protozoan parasites causing leishmaniasis in humans and animals. The aim of the study was to analyse the epidemiology of leishmaniasis in Turkey, Azerbaijan and Georgia from 2005 to 2020 and evaluate the associated risk for disease emergence in European countries. It is based on an analysis of WHO and OIE reported cases between 2005 and 2020, a review of scientific articles published in SCOPUS between 2009 and 2020 and a questionnaire survey to public health and veterinary authorities in these countries. Endemic *Leishmania* spp. include *L. infantum* in the three countries, *L. major* in Azerbaijan and Turkey and *L. tropica* and *L. donovani* in Turkey. Leishmaniasis is reported in humans, animals and sand flies and incidence is spatially and temporarily variable. In the southern Caucasus and particularly in Georgia, reported incidence of human visceral leishmaniasis by *L. infantum* remains high. However, whilst Georgia experienced a gradual decrease from >4.0 cases per 100,000 population in 2005-09 to 1.13 cases per 100,000 population in 2020, the period with highest incidence in Azerbaijan, which ranged between 0.40 and 0.61 cases per 100,000 population, was 2016-2019, and no cases have so far been reported for 2020. Visceral leishmaniasis in the Southern Caucasus affects mostly young children from deprived urban areas and its closely associated to canine leishmaniasis. Turkey reported cases of visceral leishmaniasis between 2005 and 2012 and in 2016 only, and incidence ranged between 0.02 and 0.05 per 100,000 population. In contrast, the reported annual incidence of cutaneous leishmaniasis in Turkey was much greater and peaked at 7.02 cases per 100,000 population in 2013, associated to imported cases from cutaneous leishmaniasis endemic Syria. Leishmaniasis by *L. infantum* in Azerbaijan and Georgia represents a regional public and animal health challenge that requires support to improve diagnosis, treatment and control. The unprecedented rise of cutaneous leishmaniasis and the spread of *L. tropica* and *L. donovani* in Turkey is an important risk factor for their emergence in Europe, especially in Mediterranean countries where competent vectors are widespread.

### Parasitological and immunological evaluation of a quinoline derivative salt incorporated into a polymeric micelle formulation against *Leishmania infantum* infection.

Ribeiro Antinarelli, L., Glanzmann, N., Mendonça, D., Lage, D., Oliveira-da-Silva, J., Tavares, G., Carvalho, A., Freitas, C.,

Martins, V., Duarte, M., Menezes-Souza, D., da Silva, A., Coelho, E., Soares Coimbra, E.

26-05-2022

*Parasitol Res*

<https://doi.org/10.1007/s00436-022-07544-1>

Leishmaniasis is a parasitic disease caused by *Leishmania* protozoa, which presents a large spectrum of clinical manifestations. In the present study, a quinoline derivative salt named N-(2-((7-chloroquinolin-4-yl)amino)ethyl)-N-(prop-2-yn-1-yl)prop-2-yn-1-aminium chloride or QDS3 was in vitro and in vivo tested against *L. infantum* by means of its incorporation in Poloxamer 407-based polymeric micelles (QDS3/M). The in vitro antileishmanial activity of QDS3 and QDS3/M was investigated in *L. infantum* promastigotes, axenic amastigotes and infected macrophages. BALB/c mice were infected with *L. infantum*, and parasitological parameters were evaluated 1 and 15 days post-treatment by determining the parasite load by a limiting dilution assay, besides a quantitative PCR (qPCR) method. Immunological response was assessed based on production of cellular cytokines, as well as by quantification of nitrite levels and specific antibodies. In vitro results showed that QDS3 free or in micelles presented effective antileishmanial action against both parasite stages, being more effective in amastigotes. In vivo data showed that treatment using QDS3 or QDS3/M reduced the parasite load in the livers, spleens, draining lymph nodes (dLN) and bone marrows of the treated animals, 1 and 15 days after treatment, when compared to values found in the control groups. Additionally, treated mice developed a polarized Th1-type immune response, with higher levels of IL-12, IFN- $\gamma$ , GM-CSF and nitrite, besides high production of specific IgG2a antibodies, when compared to the controls. Parasitological and immunological data obtained using the micellar composition were better than the others. In conclusion, QDS3, mainly when applied in a delivery adjuvant system, could be considered for future studies as therapeutic candidate against VL.

### Erysipeloid cutaneous leishmaniasis: a study of 40 cases of an unusual variant.

Kouki, C., Masmoudi, A., Kammoun, N., Sellami, K., Saguem, I., Bahloul, E., Boudaya, S., Chikhrouhou, F., Amouri, M., Msseidi, M., Ayedi, A., Boudawara, T., Turki, H.

24-05-2022

*Int J Dermatol*

<https://doi.org/10.1111/ijd.16278>

**Background:** Erysipeloid cutaneous leishmaniasis (ECL) is known as the chronic form of cutaneous leishmaniasis (CL). However, keeping its clinical presentation in view, there is a need to revisit this form of the disease. **Aims:** To describe ECL in view of clinical features and treatment modalities. **Methods:** We include a case series seen in Sfax (Southern Tunisia) from January 2017 to January 2021. All patients clinically suggestive and laboratory confirmed with a diagnosis of CL were registered. Patients of all age groups and of either gender having cutaneous lesions resembling erysipela on the face were included in the study. Different demographic features of

the patients and clinical aspects were identified. Descriptive statistics were used for analysis. **Results:** Of 1300 registered patients with CL, 40 (3%) were diagnosed as ECL. Ages ranged from 15 to 65 years, and duration of lesions varied from 15 to 180 days. All patients had lesions over the face. Clinically, a painful infiltrated inflammatory placard of the central facial area with a butterfly shape was observed in 14 cases, as well as zones of the cheekbone (11 cases), cheekbone and nose (5 cases), cheekbone and eyelid (8 cases), and cheekbone with ear (2 cases). Several therapeutic methods were prescribed with a sufficient result with no recurrence. **Conclusion:** ECL is a rare presentation that typically occurs on the face, looking like erysipelas, in patients who are native from an endemic region of CL.

### Activity of alkaloids from *Aspidosperma nitidum* against *Leishmania (Leishmania) amazonensis*.

do Socorro Silva da Veiga, A., Silveira, F., da Silva, E., Júnior, J., Araújo, S., Campos, M., do Rosário Marinho, A., Brandão, G., Vale, V., Percário, S., Dolabela, M.

23-05-2022

*Sci Rep*

<https://doi.org/10.1038/s41598-022-12396-x>

This study evaluated the morphological changes caused by fractions and subfractions, obtained from barks of *Aspidosperma nitidum*, against *L. (L.) amazonensis* promastigotes. The ethanolic extract (EE) obtained through the maceration of trunk barks was subjected to an acid-base partition, resulting the neutral (FN) and the alkaloid (FA) fractions, and fractionation under reflux, yielded hexane (FrHEX), dichloromethane (FrDCL), ethyl acetate (FrAcOET), and methanol (FrMEOH) fractions. The FA was fractionated and three subfractions (SF5-6, SF8, and SF9) were obtained and analyzed by HPLC-DAD and <sup>1</sup>H NMR. The antipromastigote activity of all samples was evaluated by MTT, after that, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) for the active fractions were performed. Chromatographic analyzes suggest the presence of alkaloids in EE, FN, FA, and FrDCL. The fractionation of FA led to the isolation of the indole alkaloid dihydrocorynantheol (SF8 fractions). The SF5-6, dihydrocorynantheol and SF-9 samples were active against promastigotes, while FrDCL was moderately active. The SEM analysis revealed cell rounding and changes in the flagellum of the parasites. In the TEM analysis, the treated promastigotes showed changes in flagellar pocket and kinetoplast, and presence of lipid inclusions. These results suggest that alkaloids isolated from *A. nitidum* are promising as leishmanicidal.

### 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.

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*J Antimicrob Chemother*

<https://doi.org/10.1093/jac/dkac065>

**Background:** 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. **Objectives:** 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. **Methods:** 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. **Results:** 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. **Conclusions:** 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.

### Efficacy of Systemic Treatment for *Leishmania tropica* Cutaneous Leishmaniasis.

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

24-05-2022

*Acta Derm Venereol*

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

The effectiveness of systemic treatment for *Leishmania tropica* cutaneous leishmaniasis remains unclear. The purpose of the study is to evaluate the efficacy and safety of systemic treatments for *L. tropica* cutaneous leishmaniasis. This retrospective study was performed in 114 patients. Systemic treatments included liposomal amphotericin B and sodium stibogluconate. All patients underwent systemic treatment for *L. tropica* cutaneous leishmaniasis. Favourable treatment responses were recorded in 72.5% and 70.2% of the patients in the liposomal amphotericin B and sodium stibogluconate groups, respectively; 25.3% and 46% of those in the liposomal amphotericin B and sodium stibogluconate 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. Liposomal amphotericin B was associated with a shorter intravenous treatment duration and better safety profile. Thus, liposomal amphotericin B is the treatment of choice for *L. tropica* cutaneous leishmaniasis.

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## CYSTICERCOSE

### Sub-lineages of *Taenia solium* Asian Genotype Recorded in North India.

Moudgil, P., Kumar, R., Jindal, N., Moudgil, A.

26-05-2022

*Acta Parasitol*

<https://doi.org/10.1007/s11686-022-00564-y>

**Purpose:** Porcine cysticercosis is a neglected zoonotic disease of significant veterinary and medical importance owing to its economic impact and public health significance. The present study aimed at genetic characterization of *Taenia solium* metacestodes in slaughtered pigs of Haryana (North India).

**Methods:** A total of 213 (160 and 53 from Chandigarh and Hisar, respectively) slaughtered pigs intended for human consumption were screened for the presence of *T. solium* metacestodes. The retrieved metacestodes were confirmed molecularly based on the partial amplification of mitochondrial cytochrome c oxidase subunit 1 (CO1) gene. Evolutionary divergence, haplotype and nucleotide diversities and neutrality indices of the retrieved isolates were also assessed. **Results:** Out of the 213 pigs, 2 (0.94%) revealed the presence of metacestodes involving 1 pig each from Chandigarh (0.62%) and Hisar (1.9%). The sequences obtained after custom sequencing were submitted to GenBank under the accession numbers LC661682-83. The present study haplotype clustered with haplotypes of Asian origin and showed variation from other haplotypes by 1-23 mutational steps. However, the present study isolates also showed nucleotide polymorphisms (A198T, A199G, A201T, G204A, T206A, C210T, T212G, T213A, T216G/A, T217C, T221C, C524T, G994A) at different positions, which indicated the presence of sub-lineages. Low nucleotide diversity ( $\pi=0.020$ ) and negative value of Tajima's D (-1.304) observed for the haplotypes under consideration was indicative of purifying selection and recent population expansion. **Conclusions:** Our study confirms the circulation of *T. solium* Asian genotype (with distinct sub-lineages) in study area and recommends strict control measures to contain the zoonotic disease.

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## DRACUNCULOSE

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## ECHINOCOCCOSE

### Determination of extracellular traps structures from sheep polymorphonuclear leukocytes to *Echinococcus granulosus* protoscoleces.

Yildiz, K., Sursal Simsek, N., Gurcan, I.

27-05-2022

*Exp Parasitol*

<https://pubmed.ncbi.nlm.nih.gov/35636497>

It was aimed to detect extracellular traps structures from sheep polymorphonuclear leukocytes (PMN) after being confronted with *Echinococcus granulosus* protoscoleces in vitro. Also, the effect of cyst fluid was examined on the development of extracellular traps. At the end of the incubation for 1 h, the extracellular traps augmented with neutrophil elastase, histone (H3) and myeloperoxidase were visualized in the protoscoleces-PMN co-culture microscopically. Some protoscoleces lysed and the chitinous hooks released were surrounded by the extracellular traps. The other protoscoleces were still intact and the extracellular trap structures were observed around them. The relationship between the extracellular DNA contents and the protoscoleces concentration was not found statistically significant ( $P > 0.05$ ). The extracellular DNA amount in the co-cultures diluted in RPMI-1640 increased with the incubation time ( $P < 0.05$ ). However, the time-dependent relationship was not found in the co-cultures diluted in the cyst fluid ( $P > 0.05$ ). The difference in the extracellular DNA amount was detected as statistically significant ( $P < 0.05$ ) between the two co-culture groups (diluted in RPMI-1640 or the cyst fluid), except for 30 min incubation. To the Author's knowledge, NETosis reaction was firstly observed in sheep PMN after being confronted with protoscoleces in vitro. The cyst fluid had some negative effects on the development of extracellular traps from sheep PMNs at the 1-h incubation time. It should be investigated which molecules are responsible for NETosis inhibition in hydatid cyst fluid. Future studies may clarify whether neutrophils fight with protoscoleces by using their different mechanisms.

### Electrical potentials of protoscoleces of the cestode *Echinococcus granulosus* from bovine origin.

Carabajal, M., Durán, M., Olivera, S., Fernández Salom, M., Cantiello, H.

27-05-2022

*Exp Parasitol*

<https://pubmed.ncbi.nlm.nih.gov/35636496>

Larval stages of taeniid *Echinococcus granulosus* are the infective forms of cystic echinococcosis or hydatidosis, a worldwide zoonosis. The protoscolex that develops into the

adult form in the definitive host is enveloped by a complex cellular syncytial tegument, where all metabolic interchange takes place. Little information is available as to the electrical activity of the parasite in this developmental stage. To gain insight into the electrical activity of the parasite at the larval stage, we conducted microelectrode impalements of bovine lung protoscoleces (PSCs) of *Echinococcus granulosus* in standard saline solution. We observed two distinct intra-parasitic potentials, a transient peak potential, and a stable second potential, most likely representing tegumental and intra-parasitic extracellular space electrical potential differences. These values changed on the developmental status of the parasite, its anatomical regions, or time course after harvesting. Changes in electrical potential differences of the parasite provide an accessible and valuable parameter for the study of transport mechanisms and potential targets for developing novel antiparasitic therapeutics.

### Assessment of echinococcosis control in Tibet Autonomous Region, China.

Wang, L., Gongsang, Q., Pang, H., Qin, M., Wang, Y., Li, J., Frutos, R., Gavotte, L.

26-05-2022

*Infect Dis Poverty*

<https://doi.org/10.1186/s40249-022-00987-9>

**Background:** In China the highest prevalence of echinococcosis is in Tibet Autonomous Region (TAR). The government has issued documents and implemented comprehensive prevention and control measures focusing on controlling the source of infection of echinococcosis. It was very important to understand the implementation and effect of infectious source control measures. The purpose of this study was to examine the implementation of measures to control infectious source (domestic and stray dogs) in TAR and to assess their effectiveness. **Methods:** We collected data on domestic dog registration and deworming and stray dog sheltering in 74 counties/districts in the TAR from 2017 to 2019. Fecal samples from domestic dogs were collected from randomly selected towns to determine *Echinococcus* infection in dogs using coproantigen ELISA. We analyzed the data to compare the canine rate of infection between 2016 and 2019. The data analysis was performed by SPSS statistical to compare dog infection rate in 2016 and 2019 by chi-square test, and ArcGIS was used for mapping. **Results:** From 2017 to 2019, 84 stray dog shelters were built in TAR, and accumulatively 446,660 stray or infected dogs were arrested, sheltered, or disposed of. The number of domestic dogs went downward, with an increased registration management rate of 78.4% (2017), 88.8% (2018), and 99.0% (2019). Dogs were dewormed 5 times in 2017, 12 times in 2018, and 12 times in 2019. The dog infection rate was 1.7% (252/14,584) in 2019, significantly lower than 7.3% (552/7564) from the survey of echinococcosis prevalence in Tibet in 2016 ( $P < 0.05$ ). **Conclusion:** Between 2017 and 2019, the number of stray dogs and infection rate of *Echinococcus* spp. in domestic dogs decreased significantly, indicating that dogs were effectively controlled as a source of infection in TAR and reflecting a significant decrease in the risk

of echinococcosis transmission.

### Primary pelvic hydatid cyst causing acute urinary retention.

Dua, B., Sharma, R., Tiwari, T., Goyal, S.

25-05-2022

*BMJ Case Rep*

<https://pubmed.ncbi.nlm.nih.gov/35613836>

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

### Liver function markers and haematological dynamics during acute and chronic phases of experimental *Fasciola hepatica* infection in cattle treated with triclabendazole.

Costa, M., Saravia, A., Ubios, D., Lores, P., da Costa, V., Festari, M., Landeira, M., Rodríguez-Zraquía, S., Banchoero, G., Freire, T.

30-05-2022

*Exp Parasitol*

<https://pubmed.ncbi.nlm.nih.gov/35654132>

*Fasciola hepatica*, a worldwide-distributed liver fluke, is one of the causative agents of fasciolosis, a zoonotic disease that affects livestock and humans. In livestock, fasciolosis causes huge economic losses worldwide, reducing animal fertility, milk production, weight gain and condemnation of livers. In spite of the availability of drugs, such as triclabendazole (TCZ), for the treatment of fasciolosis, they do not necessarily prevent liver damage or parasite reinfection and can eventually increase parasite resistance. The aim of this research was to relate the hepatic function, haematological parameters, leukocyte counts in circulation and parasite egg shedding during *F. hepatica* acute and chronic phases of infection in cattle as well as to determine how these parameters change with TCZ-treatment of chronically infected cattle. Our results show that increased levels of serum aspartate aminotransferase (AST) and gamma glutamyltransferase (GGT) were detected in early stages of the experimental infection. Moreover, high circulating eosinophil count and plateletcrit levels were correlated with fluke number in livers from infected cattle. On the other hand, although TCZ-treatment in the chronic phase of infection reduced parasite burden and damage in the liver, it was not able to completely avoid them. In conclusion, our work sheds light into the physiopathological mechanisms induced during fluke infection in cattle, revealing the complexity of the host response to the infection, together with the effects of TCZ-treatment in chronically infected animals.

### **Epidemiology and determinants of *Clonorchis sinensis* infection: a community-based study in southeastern China.**

**Qian, M., Zhou, C., Jiang, Z., Yang, Y., Lu, M., Wei, K., Wei, S., Chen, Y., Li, H., Zhou, X.**

29-05-2022

*Acta Trop*

<https://pubmed.ncbi.nlm.nih.gov/35649496>

Clonorchiasis is caused by the ingestion of raw freshwater fish and causes high burden in East Asia. The epidemiological profiles and determinants of *C. sinensis* infection, knowledge, practice and attitude related to clonorchiasis were demonstrated in Hengxian county, Guangxi, China. The overall prevalence of *C. sinensis* was 60.3%, which was higher in male than in female and in elder population compared to children. The percentage knowing local transmission, transmission route and harm of *C. sinensis* was 20.9%, 31.4% and 32.5%. A percentage of 60.4% reported ingestion of raw freshwater fish, while 70.1% persons would like to accept treatment if infected with *C. sinensis*. Of the individuals ingesting raw freshwater fish, 82.0% did at home and 81.3% drunk alcohol when ingesting raw freshwater fish. Sixty-two percent showed the persistence on ingestion of raw freshwater fish in future. The ingestion of raw freshwater fish varied by seasons, with a proportion of 57.8% in spring, 48.3% in summer, 60.2% in autumn and 92.2% in winter. In multivariable regression models, age groups, history with *C. sinensis* treatment, and frequency on ingesting raw freshwater fish were related to *C. sinensis* infection, while gender, educational level, history with *C. sinensis* infection, and knowing local transmission were related to the practice of ingesting raw freshwater fish. Gender, history with *C. sinensis* treatment, frequency on ingesting raw freshwater fish, duration of ingesting raw freshwater fish and drinking alcohol when ingesting raw freshwater fish were associated to the attitude to the ingestion of raw freshwater fish in future. Great efforts are needed to combat clonorchiasis, in which the heterogeneity of population in knowledge, practice, attitude and infection needs to be considered. Men are of crucial importance in term of the morbidity control through chemotherapy. Meanwhile, massive education is expected to implement, which needs to promote the change of ingesting raw freshwater fish for sustainable control of clonorchiasis.

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## **FILARIOSE LYMPHATIQUE**

### **A refined and updated health impact assessment of the Global Programme to Eliminate Lymphatic Filariasis (2000-2020).**

**Turner, H., Ottesen, E., Bradley, M.**

28-05-2022

*Parasit Vectors*

<https://doi.org/10.1186/s13071-022-05268-w>

**Background:** Lymphatic filariasis (LF) is a neglected tropical disease (NTD). In 2000 the World Health Organization (WHO) established the Global Programme to Eliminate Lymphatic Filariasis (GPELF). A key component of this programme is mass drug administration (MDA). Between 2000 and 2020, the GPELF has delivered over 8.6 billion treatments to at-risk populations. The last impact assessment of the programme evaluated the treatments provided between 2000-2014. The goal of this analysis is to provide an updated health impact assessment of the programme, based on the numbers treated between 2000-2020. **Methods:** We updated and refined a previously established model that estimates the number of clinical manifestations and disability-adjusted life years (DALYs) averted by the treatments provided by the GPELF. The model comprises three different population cohorts that can benefit from MDA provided (those protected from acquiring infection, those with subclinical morbidity prevented from progressing and those with clinical disease alleviated). The treatment numbers were updated for all participating countries using data from the WHO. In addition, data relating to the estimated number of individuals initially at risk of LF infection were updated where possible. Finally, the DALY calculations were refined to use updated disability weights. **Results:** Using the updated model and corresponding treatment data, we projected that the total benefit cohort of the GPELF (2000-2020) would consist of approximately 58.5 million individuals and the programme would avert 44.3 million chronic LF cases. Over the lifetime of the benefit cohorts, this corresponded to 244 million DALYs being averted. **Conclusion:** This study indicates that substantial health benefits have resulted from the first 20 years of the GPELF. It is important to note that the GPELF would have both additional benefits not quantified by the DALY burden metric as well as benefits on other co-endemic diseases (such as soil-transmitted helminths, onchocerciasis and scabies)-making the total health benefit underestimated. As with the past impact assessments, these results further justify the value and importance of continued investment in the GPELF.

### **Canine filaria species in selected lymphatic filariasis endemic and non-endemic areas in Sri Lanka.**

**Rathnayake, S., Chandrasena, N., Wijerathna, T., Mallawarachchi, H., Gunathilaka, N.**

26-05-2022

*Parasitol Res*

<https://doi.org/10.1007/s00436-022-07555-y>

Subperiodic brugian filariasis and dirofilariasis show a rising trend in Sri Lanka posing a threat to public health. As information was limited on canine filaria species in Sri Lanka, we studied the filaria parasites among dog populations in lymphatic filariasis (LF) endemic and non-endemic regions by microscopy and molecular methods. Thick blood smears (TBSs) were performed among 295 dogs presenting to veterinary clinics for surgical or sterilization procedures in Galle (LF endemic) and Mullaitivu (LF non-endemic) districts,

of which 55.6% were positive for any microfilariae. We identified *Dirofilaria repens* (50.8%) and *Brugia* spp. (20.6%) by microscopy, which, included mono-infections (*D. repens* 35.3% and *Brugia* spp. 5%) and co-infections (15.6%). Infections in Galle and Mullaitivu were 61% and 44.9% respectively. The brugian filariasis rate was significantly higher among canines in LF endemic Galle district (29.9%) than in Mullaitivu (LF non-endemic) (1.1%) ( $P < 0.001$ ), while *D. repens* infections were comparable in both districts. Genomic DNA extracted from 10% of microfilariae positive TBs was amplified using pan-filarial primers targeting the internal-transcriber-spacer region-2 (ITS-2). Sequencing of amplicons confirmed the presence of *D. repens* (89.28%), *Brugia pahangi* (7.14%) and *B. malayi* (3.57%) infections. The phylogeny constructed and analysed in MEGA X indicated genetic variability among *D. repens* and *B. pahangi* isolates from Sri Lanka. With this study, we were able to report *B. pahangi* infections for the first time in Sri Lanka.

iodoquinol were the only compounds with activity against causative agents from the three different fungal skinNTDs. Fungal melanin inhibition enhanced the activity of antifungal agents. For mycetoma, the fenarimols, aminothiazoles and benzimidazole carbamates are currently being investigated in the MycetOS initiative. To come to a more integrated approach to identify drugs active against all three fungal skinNTDs, compounds made in the MycetOS initiative could also be explored for chromoblastomycosis and sporotrichosis.

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## MYCETOME

### Visual ethnographic documentation: a novel tool for mycetoma awareness and advocacy.

Fahal, A., Otieno, L., Ahmed, E., Kashif, T., Khalid, M., Mahmoud, A., Ododo, L., Kyalo, T., Bakhiet, S.  
30-05-2022

*Trans R Soc Trop Med Hyg*

<https://pubmed.ncbi.nlm.nih.gov/35640654>

### Identifying novel drugs with new modes of action for neglected tropical fungal skin diseases (fungal skinNTDs) using an Open Source Drug discovery approach.

Lim, W., Verbon, A., van de Sande, W.  
25-05-2022

*Expert Opin Drug Discov*

<https://doi.org/10.1080/17460441.2022.2080195>

**Introduction:** The three fungal skin neglected tropical diseases (NTD) mycetoma, chromoblastomycosis and sporotrichosis currently lack prioritization and support to establish drug discovery programs in search for novel treatment options. This has made the efforts to identify novel drugs for these skinNTDs fragmented. **Areas covered:** To help escalate the discovery of novel drugs to treat these fungal skinNTDs, the authors have prepared an overview of the compounds with activity against fungal skinNTDs by analyzing data from individual drug discovery studies including those performed on the Medicines for Malaria Venture (MMV) open access boxes. **Expert opinion:** The authors were unable to identify studies in which causative agents of all three skinNTDs were included, indicating that an integrated approach is currently lacking. From the currently available data, the azoles and

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## ONCHOCERCOSE

### Crystal structure of an extracellular superoxide dismutase from *Onchocerca volvulus* and implications for parasite-specific drug development.

Moustafa, A., Perbandt, M., Liebau, E., Betzel, C., Falke, S.  
27-05-2022

*Acta Crystallogr F Struct Biol Commun*

<https://doi.org/10.1107/S2053230X22005350>

Superoxide dismutases (SODs) are metalloproteins that are responsible for the dismutation of superoxide anion radicals. SODs are consequently protective against oxidative damage to cellular components. Among other protective mechanisms, the filarial parasite *Onchocerca volvulus* has a well developed defense system to scavenge toxic free radicals using SODs during migration and sojourning of the microfilariae and adult worms in the human body. *O. volvulus* is responsible for the neglected disease onchocerciasis or 'river blindness'. In the present study, an extracellular Cu/Zn-SOD from *O. volvulus* (OvEC-SOD) was cloned, purified and crystallized to obtain structural insight into an attractive drug target with the potential to combat onchocerciasis. The recombinant OvEC-SOD forms a dimer and the protein structure was solved and refined to 1.55 Å resolution by X-ray crystallography. Interestingly, a sulfate ion supports the coordination of the conserved copper ion. The overall protein shape was verified by small-angle X-ray scattering. The enzyme shows a different surface charge distribution and different termini when compared with the homologous human SOD. A distinct hydrophobic cleft to which both protomers of the dimer contribute was utilized for a docking approach with compounds that have previously been identified as SOD inhibitors to highlight the potential for individual structure-based drug development.

## SCHISTOSOMIASE

**[Updated recommendations on the treatment of infectious diseases in refugees in childhood and adolescence in Germany (situation as of 30 March 2022), registered as S1 guidelines (AWMF-Register Nr. 048-017)].**

Revue de littérature

**Pfeil, J., DGPI, Assaad, K., BVÖGD, von Both, U., DAKJ/Bündnis Kinder- und Jugendgesundheit, Janda, A., Kitz, C., Kobbe, R., GTP, Kunze, M., DGGG, Lindert, J., DGKCH, Ritz, N., PIGS, Trapp, S., BVKJ, Hufnagel, M., DGKJ**  
25-05-2022

*Monatsschr Kinderheilkd*

<https://doi.org/10.1007/s00112-022-01499-4>

**Background:** Based on 190,000 applications for asylum, Germany remains a top destination for refugees and asylum seekers in Europe. The updated recommendations are considered evidence-based and targeted guidelines for the diagnosis and prevention of infectious diseases in underage refugees and asylum seekers. **Objective:** The objective of these recommendations is to guide medical staff in the care of minor refugees, in particular to: 1. assure early recognition and completion of incomplete vaccination status, 2. diagnose and treat common infectious diseases, 3. recognize and treat imported infectious diseases that are considered uncommon to the German healthcare system. **Material and methods:** The recommendations have been formally written to be published as AWMF S1 guidelines. This includes a representative expert panel appointed by several professional societies, and formal adoption of the recommendations by the board of directors of all societies concerned. **Results:** Recommendations are given for the medical evaluation of minor refugees, including medical history and physical examination. A blood count as well as screening for tuberculosis and hepatitis B should be offered to all minor refugees. In addition, screening for other infectious diseases like hepatitis C, HIV or schistosomiasis should be considered depending on age and country of origin. Vaccinations are recommended based on both age and country of origin. **Conclusion:** As thousands of minor refugees continue to seek shelter in Germany every year, professional health care with adequate financial support needs to be established to ensure an appropriate medical treatment of this particularly vulnerable population.

### **Predictors of bovine *Schistosoma japonicum* infection in rural sichuan, china.**

**Grover, E., Paull, S., Kechris, K., Buchwald, A., James, K., Liu, Y., Carlton, E.**  
26-05-2022

*Int J Parasitol*

<https://pubmed.ncbi.nlm.nih.gov/35644269>

In China, bovines are believed to be the most common animal source of human schistosomiasis infections, though little is known about what factors promote bovine infections. The

current body of literature features inconsistent, and sometimes contradictory results, and to date, few studies have looked beyond physical characteristics to identify the broader environmental conditions that predict bovine schistosomiasis. Because schistosomiasis is a sanitation-related, water-borne disease transmitted by many animals, we hypothesized that several environmental factors - such as the lack of improved sanitation systems, or participation in agricultural production that is water-intensive - could promote schistosomiasis infection in bovines. Using data collected as part of a repeat cross-sectional study conducted in rural villages in Sichuan, China from 2007 to 2016, we used a Random Forests, machine learning approach to identify the best physical and environmental predictors of bovine *Schistosoma japonicum* infection. Candidate predictors included: (i) physical/biological characteristics of bovines, (ii) human sources of environmental schistosomes, (iii) socio-economic indicators, (iv) animal reservoirs, and (v) agricultural practices. The density of bovines in a village and agricultural practices such as the area of rice and dry summer crops planted, and the use of night soil as an agricultural fertilizer, were among the top predictors of bovine *S. japonicum* infection in all collection years. Additionally, human infection prevalence, pig ownership and bovine age were found to be strong predictors of bovine infection in at least 1 year. Our findings highlight that presumptively treating bovines in villages with high bovine density or human infection prevalence may help to interrupt transmission. Furthermore, village-level predictors were stronger predictors of bovine infection than household-level predictors, suggesting future investigations may need to apply a broad ecological lens to identify potential underlying sources of persistent transmission.

### **Performance of a rapid immuno-chromatographic test (*Schistosoma* ICT IgG-IgM) for detecting *Schistosoma*-specific antibodies in sera of endemic and non-endemic populations.**

**Hoermann, J., Kuenzli, E., Schaefer, C., Paris, D., Bühler, S., Odermatt, P., Sayasone, S., Neumayr, A., Nickel, B.**  
27-05-2022

*PLoS Negl Trop Dis*

<https://doi.org/10.1371/journal.pntd.0010463>

**Background:** Schistosomiasis, an acute and chronic parasitic disease caused by human pathogenic *Schistosoma* species, is a neglected tropical disease affecting more than 220 million people worldwide. For diagnosis of schistosomiasis, stool and urine microscopy for egg detection is still the recommended method, however sensitivity of these methods is limited. Therefore, other methods like molecular detection of DNA in stool, detection of circulating cathodic antigen in urine or circulating anodic antigen in urine and serum, as well as serological tests have gained more attention. This study examines the sensitivity and specificity of a rapid diagnostic test based on immunochromatography (*Schistosoma* ICT IgG-IgM, LD Bio, Lyon, France) for simultaneous detection of specific IgG and IgM antibodies in serum, against *Schistosoma*

spp. in endemic and non-endemic populations. **Methodology/Principal findings:** Frozen banked serum samples from patients with confirmed schistosomiasis, patients with other helminth infections, patients with seropositive rheumatoid arthritis and healthy blood donors were used to assess the sensitivity and the specificity of the Schistosoma ICT IgG-IgM rapid diagnostic test. The test showed a sensitivity of 100% in patients with parasitologically confirmed schistosomiasis, irrespective of the species (*S. mansoni*, *S. haematobium*, *S. japonicum*, *S. mekongi*). In healthy blood donors and patients with rheumatoid factor positive rheumatoid arthritis from Europe, specificity was 100%. However, in serum samples of patients with other tissue invasive helminth infections, the test showed some cross-reactivity, resulting in a specificity of 85%. **Conclusion/Significance:** With its high sensitivity, the Schistosoma ICT IgG-IgM rapid diagnostic test is a suitable screening test for detection of Schistosoma specific antibodies, including *S. mekongi*. However, in populations with a high prevalence of co-infection with other tissue invasive helminths, positive results should be confirmed with other diagnostic assays due to the test's imperfect specificity.

### A new ferritin SjFer0 affecting the growth and development of Schistosoma japonicum.

Zeng, F., Yi, C., Zhang, W., Cheng, S., Sun, C., Luo, F., Feng, Z., Hu, W.

24-05-2022

Parasit Vectors

<https://doi.org/10.1186/s13071-022-05247-1>

**Background:** Schistosomiasis, an acute and chronic parasitic disease, causes substantial morbidity and mortality in tropical and subtropical regions of the world. Iron is an essential constituent of numerous macromolecules involving in important cellular reactions in virtually all organisms. Trematodes of the genus *Schistosoma* live in iron-rich blood, feed on red blood cells and store abundant iron in vitelline cells. Ferritins are multi-meric proteins that store iron inside cells. Three ferritin isoforms in *Schistosoma japonicum* are known, namely SjFer0, SjFer1 and SjFer2; however, their impact on the growth and development of the parasites is still unknown. In this study we report on and characterize the ferritins in *S. japonicum*. **Methods:** A phylogenetic tree of the SjFer0, SjFer1 and SjFer2 genes was constructed to show the evolutionary relationship among species of genus *Schistosoma*. RNA interference in vivo was used to investigate the impact of SjFer0 on schistosome growth and development. Immunofluorescence assay was applied to localize the expression of the ferritins. RNA-sequencing was performed to characterize the iron transport profile after RNA interference. **Results:** SjFer0 was found to have low similarity with SjFer1 and SjFer2 and contain an additional signal peptide sequence. Phylogenetic analysis revealed that SjFer0 can only cluster with some ferritins of other trematodes and tapeworms, suggesting that this ferritin branch might be unique to these parasites. RNA interference in vivo showed that SjFer0 significantly affected the growth and development

of schistosomula but did not affect egg production of adult female worms. SjFer1 and SjFer2 had no significant impact on growth and development. The immunofluorescence study showed that SjFer0 was widely expressed in the somatic cells and vitelline glands but not in the testicle or ovary. RNA-sequencing indicated that, in female, the ion transport process and calcium ion binding function were downregulated after SjFer0 RNA interference. Among the differentially downregulated genes, Sj-cpi-2, annexin and insulin-like growth factor-binding protein may be accounted for the suppression of schistosome growth and development. **Conclusions:** The results indicate that SjFer0 affects the growth and development of schistosomula but does not affect egg production of adult female worms. SjFer0 can rescue the growth of the fet3fet4 double mutant *Saccharomyces cerevisiae* (strain DEY1453), suggesting being able to promote iron absorption. The RNA interference of SjFer0 inferred that the suppression of worm growth and development may via down-regulating Sj-cpi-2, annexin, and IGFBP.

### Human tumor necrosis factor alpha affects the egg-laying dynamics and glucose metabolism of Schistosoma mansoni adult worms in vitro.

Lopes-Junior, E., Bertevello, C., de Oliveira Silveira, G., Guedes, C., Rodrigues, G., Ribeiro, V., Amaral, M., Kanamura, C., Pinto, P., Krüger, R., Verjovski-Almeida, S., Oliveira, K.

24-05-2022

Parasit Vectors

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Several studies have described the effects of human tumor necrosis factor alpha (hTNF- $\alpha$ ) on *Schistosoma mansoni*. hTNF- $\alpha$  affects the worm's development, metabolism, egg-laying, gene expression and protein phosphorylation. The available data on the influence of hTNF- $\alpha$  on egg-laying in *S. mansoni* are controversial, but understanding the mechanism of egg-laying regulation in this species is essential in combating schistosomiasis. We characterized the effects of in vitro treatment of *S. mansoni* adult worms with different doses of hTNF- $\alpha$  (5, 20 and 40 ng/ml) for 5 days. We explored the effects on egg-laying rate, glucose levels, ATP metabolism, and messenger RNA (mRNA) expression levels of lactate dehydrogenase, glucose transporters and the parasite gene which acts as an hTNF- $\alpha$  receptor, SmTNFR. hTNF- $\alpha$  influenced egg-laying in a time- and dose-dependent manner: at a dose of 40 ng/ml, egg-laying increased on day 2 and decreased on days 3 and 4; at 20 ng/ml, egg-laying decreased on day 3; while at 5 ng/ml, egg-laying decreased on day 4. The total number of eggs produced was not affected by the different treatments, but the egg-laying dynamics were: the median egg-laying time decreased significantly with treatment, and egg developmental stages and size were also affected. At 5 and 20 ng/ml hTNF- $\alpha$ , lactate production diminished on day 3 up to day 5, while glucose uptake increased on day 5. At 40 ng/ml, glucose uptake diminished on day 1 up to day 3, while ATP accumulation was detected on day 5. No significant changes in mRNA expression were detected in any of the treatments. We found that crosstalk involving hTNF- $\alpha$  and

parasite signaling plays a role in the fine-scale regulation of the worm's metabolism and physiology, and points to new strategies for disease control.

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

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GALE

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### MORSURES DE SERPENT

#### **Role of Toll-like receptors in local effects in a model of experimental envenoming induced by *Bothrops jararacussu* snake venom and by two phospholipases A<sub>2</sub>.**

Fontana, B., Soares, A., Zuliani, J., Gonçalves, G.  
27-05-2022

*Toxicon*

<https://pubmed.ncbi.nlm.nih.gov/35636533>

Literature shows that phospholipases A<sub>2</sub> isolated from snake venoms of the genus *Bothrops* are involved in the local inflammatory response. However, the mechanisms by which these enzymes trigger this process have not yet been clarified. Toll-Like receptors (TLRs) are transmembrane proteins that recognize pathogens associated molecular patterns (PAMPs), or even damage associated molecular patterns (DAMPs). After this recognition, an innate immune response is activated resulting in cytokines liberation contributing to inflammation. Thus, the purpose of this work was to study the participation of different TLRs during the local inflammatory process induced by *B. jararacussu* snake venom and by two isolated phospholipases A<sub>2</sub>, BthTX-I or BthTX-II, from this venom in a model of experimental envenoming. For this, sub-lethal doses of *B. jararacussu* venom (BjussuV), BthTX-I or BthTX-II were injected in the gastrocnemius muscle. Myotoxic activity was evaluated by histological analysis and by quantification of plasma levels of total-creatine kinase (CK). The pro-inflammatory cytokines TNF- $\alpha$  and IL-1 $\beta$  was measured in both muscle tissue homogenate and plasma. A quantification of the gene expression of TLRs 2, 4, 5 and 9 in muscle tissue homogenate was performed by the real-time polymerase chain reaction (RTq-PCR). According to the results, it can be observed that, when compared to the control, there was a significant increase of CK and TNF- $\alpha$  in the bloodstream of the animals injected with both BjussuV, BthTX-I and BthTX-II. In

muscle tissue homogenate, it was observed a significant increase in both cytokines, TNF- $\alpha$  and IL-1 $\beta$ , levels compared to the control animals. The results point to an important increase in the gene expression of TLR2 and TLR4, suggesting that these TLRs can be important targets for the development of future therapies for local treatment for victims of snakebites.

#### **VenomMaps: Updated species distribution maps and models for New World pitvipers (Viperidae: Crotalinae).**

Rautsaw, R., Jiménez-Velázquez, G., Hofmann, E., Alencar, L., Grünwald, C., Martins, M., Carrasco, P., Doan, T., Parkinson, C.  
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*Sci Data*

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Beyond providing critical information to biologists, species distributions are useful for naturalists, curious citizens, and applied disciplines including conservation planning and medical intervention. Venomous snakes are one group that highlight the importance of having accurate information given their cosmopolitan distribution and medical significance. Envenomation by snakebite is considered a neglected tropical disease by the World Health Organization and venomous snake distributions are used to assess vulnerability to snakebite based on species occurrence and antivenom/healthcare accessibility. However, recent studies highlighted the need for updated fine-scale distributions of venomous snakes. Pitvipers (Viperidae: Crotalinae) are responsible for >98% of snakebites in the New World. Therefore, to begin to address the need for updated fine-scale distributions, we created VenomMaps, a database and web application containing updated distribution maps and species distribution models for all species of New World pitvipers. With these distributions, biologists can better understand the biogeography and conservation status of this group, researchers can better assess vulnerability to snakebite, and medical professionals can easily discern species found in their area.