



Réseau MTN Francophone

Veille scientifique Maladies tropicales négligées

Semaine 14

04 avril 2022 – 11 avril 2022

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DENGUE, CHIKUNGUNYA ET MALADIE A VIRUS ZIKA

Anxiety, depression, and quality of life in mothers of children with congenital Zika syndrome: Results of a 5-year follow-up study.

Oliveira, S., Tavares, C., Santos, V., Santos, H., Martins-Filho, P.
08-04-2022

Rev Soc Bras Med Trop

<https://pubmed.ncbi.nlm.nih.gov/35416879>

Frequency of exposure to arboviruses and characterization of Guillain Barré syndrome in a clinical cohort of patients treated at a tertiary referral center in Brasília, Federal District.

Matos, L., Borges, A., Palmeira, A., Lima, V., Maciel, E.,
Fernandez, R., Mendes, J., Romero, G.

08-04-2022

Rev Soc Bras Med Trop

<https://pubmed.ncbi.nlm.nih.gov/35416870>

Guillain Barré syndrome (GBS) is an acute autoimmune polyradiculoneuropathy often associated with previous exposure to infectious agents. A clinical cohort of 41 patients with GBS admitted to the Base Hospital Institute of the Federal District between May 2017 and April 2019 was followed up for 1 year. Serological tests for arbovirus detection and amplification of nucleic acids using polymerase chain reaction for zika virus (ZIKV), dengue virus (DENV), and chikungunya virus (CHIKV) were performed. The cohort consisted of 61% men with a median age of 40 years, and 83% had GBS-triggering events. A total of 54% had Grade 4 disability, 17% had Grade 3, 12% had Grade 2, 10% had Grade 5, and 7% had Grade 1. The classic form occurred in 83% of patients. Nerve conduction evaluations revealed acute demyelinating inflammatory polyneuropathy (51%), acute motor axonal neuropathy (17%), acute sensory-motor neuropathy (15%), and indeterminate forms (17%). Four patients were seropositive for DENV. There was no laboratory detection of ZIKV or CHIKV infection. Ninety percent of patients received human immunoglobulin. Intensive care unit admission occurred in 17.1% of the patients, and mechanical ventilation was used in 14.6%. One patient died of Bickerstaff's encephalitis. Most patients showed an improvement in disability at 10 weeks of follow-up. GBS in the Federal District showed a variable clinical spectrum, and it was possible to detect recent exposure to DENV.

Knowledge, Attitudes, Beliefs, and Practices Regarding Dengue in La Réunion Island, France.

Lamaurt, F., De Santis, O., Ramis, J., Schultz, C., Rivadeneyra, A.,
Waelli, M., Flahault, A.

06-04-2022

Int J Environ Res Public Health

<https://pubmed.ncbi.nlm.nih.gov/35410080>

Since 2017, La Réunion island has been facing a major epidemic of dengue. Despite actions carried out by the anti-vector control department, public authorities have failed to contain this epidemic. As individual involvement is key to success in vector control, we carried out a mixed-methods study on population knowledge, attitudes, beliefs, and practices (KABP) regarding dengue infection risk in La Réunion. The study combined quantitative data collected through a questionnaire administered to a representative sample of 622 people to assess the use of protective measures and the perception of severity and risk of dengue, and a sample of 336 people to assess the level of knowledge and concern about dengue, as well as qualitative data collected through semi-structured interviews among 11 individuals who had previously completed the questionnaire. The study results show that 63% of the surveyed population had a good level of knowledge associated with age, education, and socio-professional category variables-78% considered dengue to be a serious threat, and concern was estimated at 6/10, while 71% were likely to use protective measures. The interviews revealed contradictory behaviors in the implementation of recommended actions, in conflict with personal beliefs regarding respect of human body and nature. The study also revealed a loss of confidence in public authorities.

Co-circulation of Chikungunya Virus during the 2015-2017 Zika Virus Outbreak in Pernambuco, Brazil: An Analysis of the Microcephaly Epidemic Research Group Pregnancy Cohort.

Lobkowicz, L., Miranda-Filho, D., Montarroyos, U., Martelli, C.,
Barreto de Araújo, T., De Souza, W., Bezerra, L., Dhalia, R.,
Marques, E., Clemente, N., Webster, J., Vaughan, A., Webb, E.,
Brickley, E., Alencar Ximenes, R., Microcephaly Epidemic
Research Group

11-04-2022

Am J Trop Med Hyg

<https://doi.org/10.4269/ajtmh.21-0449>

Co-circulation of arthropod-borne viruses, particularly those with shared mosquito vectors like Zika (ZIKV) and Chikungunya (CHIKV), is increasingly reported. An accurate differential diagnosis between ZIKV and CHIKV is of high clinical importance, especially in the context of pregnancy, but remains challenging due to limitations in the availability of specialized laboratory testing facilities. Using data collected from the prospective pregnancy cohort study of the Microcephaly Epidemic Research Group, which followed up pregnant persons with rash during the peak and decline of the 2015-2017 ZIKV epidemic in Recife, Pernambuco, Brazil, this study aims to describe the geographic and temporal distribution of ZIKV and CHIKV infections and to investigate the extent to which ZIKV and CHIKV infections may be clinically differentiable. Between December 2015 and June 2017, we observed evidence of co-circulation with laboratory confirmation of 213 ZIKV mono-infections, 55 CHIKV mono-infections, and 58 sequential ZIKV/CHIKV infections (i.e., cases with evidence of acute ZIKV infection with concomitant

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serological evidence of recent CHIKV infection). In logistic regressions with adjustment for maternal age, ZIKV mono-infected cases had lower odds than CHIKV mono-infected cases of presenting with arthralgia (aOR, 99% CI: 0.33, 0.15-0.74), arthritis (0.35, 0.14-0.85), fatigue (0.40, 0.17-0.96), and headache (0.44, 0.19-1.90). However, sequential ZIKV/CHIKV infections complicated discrimination, as they did not significantly differ in clinical presentation from CHIKV mono-infections. These findings suggest clinical symptoms alone may be insufficient for differentiating between ZIKV and CHIKV infections during pregnancy and therefore laboratory diagnostics continue to be a valuable tool for tailoring care in the event of arboviral co-circulation.

Arbovirus outbreak in a rural region of the Brazilian Amazon.

Carvalho, V., Azevedo, R., Carvalho, V., Azevedo, R., Henriques, D., Cruz, A., Vasconcelos, P., Martins, L.

06-04-2022

J Clin Virol

<https://pubmed.ncbi.nlm.nih.gov/35405330>

An outbreak of febrile illness was reported from January to February 2018 in the Expedito Ribeiro Settlement, Santa Bárbara do Pará municipality, Pará State, Brazil. This study aimed to investigate the pathogenic agent responsible for the outbreak and the circulation of arboviruses in the region. We analyzed 94 individuals through laboratory tests for arboviruses. Forty out of 94 individuals were asymptomatic but were living with or near febrile cases, and 55 participants were symptomatic. Our results showed that 51.1% of the investigated individuals were positive for arboviruses (Oropouche, Mayaro, and Chikungunya), of which 77.8% were symptomatic. We detected 93.7% of positive cases for Oropouche infection, 2.1% for Mayaro fever, and 4.2% were positive for both Oropouche and Chikungunya infection. Oropouche virus was mainly responsible for the outbreak; however, we also detected a few Chikungunya and Mayaro fever cases. Serologic assays showed evidence of arboviruses circulation of different genera in the area.

Seroprevalence of IgG Antibodies Against Multiple Arboviruses in Bats from Cameroon, Guinea, and the Democratic Republic of Congo.

Raulino, R., Thaurignac, G., Keita, A., Esteban, A., Goumou, S., Diallo, R., Ndimbo-Kumugo, S., Ndong Bass, I., Mbala Kingebeni, P., Toure, A., Delaporte, E., Ahuka-Mundeke, S., Muyembe Tamfum, J., Mpoudi-Ngole, E., Peeters, M., Ayouba, A.

11-04-2022

Vector Borne Zoonotic Dis

<https://doi.org/10.1089/vbz.2021.0076>

Background: Emergence of mosquito-borne arboviruses has caused significant public health burden. The life cycle of arboviruses comprises sylvatic and urban cycles, including a wildlife reservoir, a human host, and an arthropod vector. However, many questions remain on the sylvatic cycles of

arboviruses. In this study, we investigate the prevalence of IgG antibodies to arboviruses of public health importance in African bats. **Material and Methods:** We collected dried blood spots from bats in Cameroon, Guinea, and the Democratic Republic of the Congo (DRC). To detect IgG antibodies to 10 antigens of 6 arboviruses (Dengue, Zika, West Nile, Usutu, Chikungunya, and O'nyong nyong viruses), we adapted a previously validated multiplex detection assay based on the Luminex technology. **Results:** We tested samples from 2579 bats, representing 1917 frugivorous and 641 insectivorous bats distributed in 7 families and 21 species. Overall, 218/2579 (8.45%) bat samples reacted with at least 1 of the 10 antigens tested. The highest prevalence was observed against Usutu virus with 2.3% (59/2579), followed by 1.9% (49/2579) and 1.35% (35/2579) for the Dengue virus serotypes 4 and 3, respectively. The global seroprevalence varied by country and collection site: 11% (151/1376) in Cameroon, 3.5% (20/565) in DRC, and 7.3% (47/638) in Guinea. The highest rates were observed in *Hypsipnathus monstrosus* (17.9%), *Rousettus aegyptiacus* (16.4%), and *Eidolon helvum* (10.7%), and in species from the insectivorous Molossidae family (7.8-8.9%). Finally, we observed changes in seroprevalence over the year in *E. helvum* and *H. monstrosus* colonies, which could be related to population structure. **Conclusion:** On more than 2500 bat samples tested, we showed variable IgG seroprevalences against multiple arboviruses. Overall, the prevalence of IgG antibodies of 8.45% against arboviruses found in bats suggest that they could play a role in arboviruses cycles in the wild, in addition to other animal species.

Has Zika Been Forgotten? Findings From Nationwide Survey on Knowledge, Attitudes, and Mosquito Preventive Practices in Malaysia.

Wong, L., Alias, H., Lee, H., AbuBakar, S.

11-04-2022

Disaster Med Public Health Prep

<https://doi.org/10.1017/dmp.2022.40>

The aim of this study is to assess knowledge and attitudes toward Zika virus disease (ZVD) as well as mosquito prevention practices in Malaysia at a nationwide level. Computer-assisted telephone interviews (CATI) were conducted between June 2019 and February 2020. There are gaps in knowledge about the symptoms, mode of transmission, and risk of microcephaly. The mean for the Zika-related knowledge score was 5.9 ($SD \pm 4.4$) out of a possible score of 14. The majority perceived little or no risk of getting ZVD (75.0%) and 75.5% were a little or not at all worried about ZVD. A high proportion reported the use of insect sprays or mosquito coils to prevent mosquito bites; however, a relatively lower proportion of people reported fixing mosquito netting on doors and windows, and using mosquito bed nets. The mean for the mosquito prevention practices score was 11.9 ($SD \pm 4.7$) out of a possible score of 27. Important factors influencing mosquito prevention practices include household income, environment factors, risk perception, and Zika-related knowledge. Zika prevention measures should be targeted in priority toward residents in lower socioeconomic neighborhoods. Campaigns

should focus on messages highlighting the high risk of getting dengue.

Mapping of molecular interactions between human E3 ligase TRIM69 and Dengue virus NS3 protease using hydrogen-deuterium exchange mass spectrometry.

Bagga, T., Tulsian, N., Mok, Y., Kini, R., Sivaraman, J.

10-04-2022

Cell Mol Life Sci

<https://doi.org/10.1007/s00018-022-04245-x>

Tripartite motif (TRIM) E3 ligases target specific substrates, including viral proteins, for proteasomal degradation, and are thus essential regulators of the innate antiviral response. TRIM69 ubiquitinates the non-structural NS3 protein of Dengue virus for its degradation by the host machinery. This antiviral strategy abrogates the immunosuppression mediated by the NS2B-NS3 protease complex. To understand how this host-driven antiviral response against Dengue virus, we sought to define the mode of interaction between human TRIM69 and Dengue NS2B-NS3 and the subsequent polyubiquitination of the protease by the E3 ligase. We show that NS2B-NS3 Δ pro is sufficient as a substrate for ubiquitination by TRIM69 using ELISA and in vitro assays. Using hydrogen-deuterium exchange mass spectrometry (HDXMS), we mapped the interface of the interaction between TRIM69 and NS2B-NS3 Δ pro, and propose a rationale for the binding and subsequent ubiquitination process. Furthermore, through sequence analysis, we showed that the regions targeted by TRIM69 on the DENV-2 NS3 protease (NS3 Δ pro) are well conserved across DENV serotypes and other flaviviruses, including Zika virus, West Nile virus, and Japanese encephalitis virus. Our results show the direct interactions of TRIM69 with viral proteins, provide mechanistic insights at a molecular level, and highlight the functional relevance of TRIM69 interacting with the Dengue viral protein. Collectively, our findings suggest that TRIM69 may act as a pan-antiflaviviral restriction factor.

Non-structural protein 1 (NS1) variants from dengue virus clinical samples revealed mutations that influence NS1 production and secretion.

Ghosh, A., Sukla, S., Nath, H., Saha, R., De, A., Biswas, S.

09-04-2022

Eur J Clin Microbiol Infect Dis

<https://doi.org/10.1007/s10096-022-04441-4>

Dengue diagnosis primarily relies on NS1 ELISA and serological (IgG/IgM) tests. There are reports of low and variable sensitivity of the widely used NS1 ELISA tests. Poor sensitivity has been attributed to patient's infection status, prevalent serotypes, and the geographical origin of the samples. We investigated whether NS1 mutations directly have any impact on NS1 ELISA-based dengue virus (DENV) detection in clinical samples. Fifty-eight serum samples were collected from dengue-endemic area during 2015-2017 and tested with three commonly used NS1 ELISA kits. The samples were subjected to

diagnostic RT-PCR and sequencing of structural gene(s). Sequencing of NS1 gene revealed amino acid changes which were transferred to respective wild type NS1 backbone to determine their effects on NS1 production and secretion in Huh-7, Vero, and A549 cells. Eighty-seven percent samples were virus RNA-positive but 65% of these were NS1 ELISA-positive. NS1-gene mutations like Val236 \rightarrow Ala (DENV2) or Trp68 \rightarrow stop codon in DENV3 were associated with decreased NS1 production and secretion. These mutations were originally identified in NS1 ELISA-negative clinical isolates. All DENV1 and > 80% DENV2 were NS1 ELISA-positive. The three NS1 ELISA could not detect recently circulating DENV3 single infections despite being RNA-positive. Among serotypes 1-3, wild-type NS1 production was highest for DENV1 and lowest for DENV3 in all cell lines tested. Mutations in circulating DENV directly correlated with NS1 production and secretion and, hence, ELISA-based NS1 detection. Further studies to define more NS1 mutations in clinical samples are needed to optimize ELISA kits for more sensitive dengue diagnosis.

Dengue NS1 induces phospholipase A₂ enzyme activity, prostaglandins, and inflammatory cytokines in monocytes.

Silva, T., Gomes, L., Jeewandara, C., Ogg, G., Malavige, G.

05-04-2022

Antiviral Res

<https://pubmed.ncbi.nlm.nih.gov/35395274>

Dengue virus (DENV) NS1 is a non-structural secretory protein associated with severe disease and known to cause vascular leak leading to dengue haemorrhagic fever (DHF). As phospholipases A₂ (PLA₂) enzymes, platelet activating factor, and leukotrienes are elevated in dengue, we sought to investigate whether NS1 potentially contributes to disease pathogenesis by inducing PLA₂s. THP-1 cells and primary human monocytes of healthy adults ($n = 6$) were co-cultured with DENV1 NS1, LPS and media alone. The latter two were used as positive and negative controls. The cell culture supernatants and lysates were harvested at 12 and 24 h and the activity of secretory and cytoplasmic PLA₂, prostaglandins (PGE₂ and PGD₂) were measured by ELISA and cytokines levels were measured using a magnetic Luminex assay. Expression of PLA2G4A, PLA2G2A, PLA2G5, PLA2G10, PLA2G7, GAPDH, NLRP3 and DDX58 genes were assessed using quantitative RT-PCR. cPLA₂ ($p = 0.005$), sPLA₂ ($p = 0.04$), PGE₂ metabolite ($p = 0.02$) and PGD₂ metabolite ($p = 0.04$) levels were significantly higher at 12 h in monocytes co-cultured with NS1. Levels of IP-10 ($p = 0.005$) and IL-10 ($p = 0.009$) was significantly higher at 24 h, whereas IFN α level was significantly higher ($p = 0.013$) only at 12 h. IL-1 β ($p = 0.028$ and $p = 0.031$) and TNF α ($p = 0.007$ and $p = 0.011$) showed significantly higher levels at both time points. At 12 h significant upregulation of PLA2G4A ($p < 0.0001$) was seen, whereas PLA2G7 ($p = <0.0001$), NLRP3 ($p = 0.0009$) and DDX58 ($p = 0.0056$) were significantly downregulated. This pattern changed at 24 h with PLA2G4A ($p = 0.0069$) showing a marked downregulation and PLA2G7, DDX58 and NLRP3 showing an upregulation, although not significant. Dengue NS1 induces

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the production of PLA₂ enzymes, prostaglandins and inflammatory cytokines from primary human monocytes, which could play a role in vascular leak in dengue.

Detection of SARS-CoV-2 antibodies in febrile patients from an endemic region of dengue and chikungunya in Peru.

Tarazona-Castro, Y., Troyes-Rivera, L., Martins-Luna, J., Cabellos-Altamirano, F., Aguilar-Luis, M., Carrillo-Ng, H., Del Valle, L., Kym, S., Miranda-Maravi, S., Silva-Caso, W., Levy-Blitchein, S., Del Valle-Mendoza, J.

08-04-2022

PLoS One

<https://doi.org/10.1371/journal.pone.0265820>

The rapid expansion of the novel SARS-CoV-2 virus has raised serious public health concerns due to the possibility of misdiagnosis in regions where arboviral diseases are endemic. We performed the first study in northern Peru to describe the detection of SARS-CoV-2 IgM antibodies in febrile patients with a suspected diagnosis of dengue and chikungunya fever. A consecutive cross-sectional study was performed in febrile patients attending primary healthcare centers from April 2020 through March 2021. Patients enrolled underwent serum sample collection for the molecular and serological detection of DENV and CHIKV. Also, serological detection of IgM antibodies against SARS-CoV-2 was performed. 464 patients were included during the study period, of which (40.51%) were positive for one pathogen, meanwhile (6.90%) presented co-infections between 2 or more pathogens. The majority of patients with mono infections were positive for SARS-CoV-2 IgM with (73.40%), followed by DENV 18.09% and CHIKV (8.51%). The most frequent co-infection was DENV + SARS-CoV-2 with (65.63%), followed by DENV + CHIKV and DENV + CHIKV + SARS-CoV-2, both with (12.50%). The presence of polyarthralgias in hands (43.75%, p<0.01) and feet (31.25%, p = 0.05) were more frequently reported in patients with CHIKV mono infection. Also, conjunctivitis was more common in patients positive for SARS-CoV-2 IgM (11.45%, p<0.01). The rest of the symptoms were similar among all the study groups. SARS-CoV-2 IgM antibodies were frequently detected in acute sera from febrile patients with a clinical suspicion of arboviral disease. The presence of polyarthralgias in hands and feet may be suggestive of CHIKV infection. These results reaffirm the need to consider SARS-CoV-2 infection as a main differential diagnosis of acute febrile illness in arboviruses endemic areas, as well as to consider co-infections between these pathogens.

Extensive public health initiatives drive the elimination of Aedes aegypti (Diptera, Culicidae) from a town in regional Queensland: A case study from Gin Gin, Australia.

Trewin, B., Montgomery, B., Hurst, T., Gilmore, J., Endersby-Harshman, N., Crisp, G.

08-04-2022

PLoS Negl Trop Dis

<https://doi.org/10.1371/journal.pntd.0010243>

Aedes aegypti is the primary vector of exotic arboviruses (dengue, chikungunya and Zika) in Australia. Once established across much of Australia, this mosquito species remains prevalent in central and northern Queensland. In 2011, Ae. aegypti was re-discovered in the town of Gin Gin, Queensland, by health authorities during routine larval surveillance. This town is situated on a major highway that provides a distribution pathway into the highly vulnerable and populous region of the state where the species was once common. Following the detection, larval habitat and adult control activities were conducted as a public health intervention to eliminate the Ae. aegypti population and reduce the risk of exotic disease transmission. Importantly, genetic analysis revealed a homogenous cluster and small effective population vulnerable to an elimination strategy. By 2015, adult surveillance revealed the population had expanded throughout the centre of the town. In response, a collaboration between research agencies and local stakeholders activated a second control program in 2016 that included extensive community engagement, enhanced entomologic surveillance and vector control activities including the targeting of key containers, such as unsealed rainwater tanks. Here we describe a model of the public health intervention which successfully reduced the Ae. aegypti population below detection thresholds, using source reduction, insecticides and novel, intensive genetic surveillance methods. This outcome has important implications for future elimination work in small towns in regions sub-optimal for Ae. aegypti presence and reinforces the longstanding benefits of a partnership model for public health-based interventions for invasive urban mosquito species.

A review on structural genomics approach applied for drug discovery against three vector-borne viral diseases: Dengue, Chikungunya and Zika.

Revue de littérature

Sundar, S., Piramanayagam, S., Natarajan, J.

08-04-2022

Virus Genes

<https://doi.org/10.1007/s11262-022-01898-5>

Structural genomics involves the advent of three-dimensional structures of the genome encoded proteins through various techniques available. Numerous structural genomics research groups have been developed across the globe and they contribute enormously to the identification of three-dimensional structures of various proteins. In this review, we have discussed the applications of the structural genomics approach towards the discovery of potential lead-like molecules against the genomic drug targets of three vector-borne diseases, namely, Dengue, Chikungunya and Zika. Currently, all these three diseases are associated with the most important global public health problems and significant economic burden in tropical countries. Structural genomics has accelerated the identification of novel drug targets and inhibitors for the treatment of these diseases. We start with

the current development status of the drug targets and antiviral drugs against these three diseases and conclude by describing challenges that need to be addressed to overcome the shortcomings in the process of drug discovery.

Virus Detection: From State-of-the-Art Laboratories to Smartphone-Based Point-of-Care Testing.

Revue de littérature

Xiao, M., Tian, F., Liu, X., Zhou, Q., Pan, J., Luo, Z., Yang, M., Yi, C.

07-04-2022

Adv Sci (Weinh)

<https://doi.org/10.1002/advs.202105904>

Infectious virus outbreaks pose a significant challenge to public healthcare systems. Early and accurate virus diagnosis is critical to prevent the spread of the virus, especially when no specific vaccine or effective medicine is available. In clinics, the most commonly used viral detection methods are molecular techniques that involve the measurement of nucleic acids or proteins biomarkers. However, most clinic-based methods require complex infrastructure and expensive equipment, which are not suitable for low-resource settings. Over the past years, smartphone-based point-of-care testing (POCT) has rapidly emerged as a potential alternative to laboratory-based clinical diagnosis. This review summarizes the latest development of virus detection. First, laboratory-based and POCT-based viral diagnostic techniques are compared, both of which rely on immunosensing and nucleic acid detection. Then, various smartphone-based POCT diagnostic techniques, including optical biosensors, electrochemical biosensors, and other types of biosensors are discussed. Moreover, this review covers the development of smartphone-based POCT diagnostics for various viruses including COVID-19, Ebola, influenza, Zika, HIV, et al. Finally, the prospects and challenges of smartphone-based POCT diagnostics are discussed. It is believed that this review will aid researchers better understand the current challenges and prospects for achieving the ultimate goal of containing disease-causing viruses worldwide.

Incidence of lab-confirmed dengue fever in a pediatric cohort in Delhi, India.

Sinha, B., Goyal, N., Kumar, M., Choudhary, A., Arya, A., Revi, A., Dutta, A., More, D., Rongsen-Chandola, T.

07-04-2022

PLoS Negl Trop Dis

<https://doi.org/10.1371/journal.pntd.0010333>

Our aim was to estimate the overall and age-specific incidence of lab-confirmed dengue fever using ELISA based assays among children 6 months to 15 years in Delhi. We enrolled a cohort of 984 children aged 6 months to <14 years in South Delhi and followed-up weekly for fever for 24 months or till 15 completed years of child-age. Households of the enrolled children were geo-tagged. NS1, IgM and IgG assays were conducted using ELISA method to confirm dengue fever

in children with ≥3 consecutive days of fever. Molecular typing was done in a subset of NS1 positive cases to identify the circulating serotypes. We had a total of 1953 person-years (PY) of follow up. Overall, there were 4208 episodes of fever with peaks during June to November. The overall incidence (95%CI) of fever was 215/100 PY (209 to 222). A total of 74/1250 3-day fever episodes were positive for acute dengue fever (NS1 and/or IgM positive). The overall incidence (95%CI) of acute dengue fever was 37.9 (29.8 to 47.6) per 1000 PY; highest among children aged 5 to 10 years (50.4 per 1000 PY, 95% CI 36.5 to 67.8). Spatial autocorrelation analysis suggested a clustering pattern for the dengue fever cases (Moran's Index 0.35, z-score 1.8, p = 0.06). Dengue PCR was positive in 16 of the 24 specimens tested; DEN 3 was the predominant serotype identified in 15/24 specimens. We found a high incidence of dengue fever among under 15-year children with clustering of cases in the community. DEN 3 was the most commonly circulating strain encountered. The findings underscore the need for development of affordable pre-vaccination screening strategy as well as newer dengue vaccines for young children while continuing efforts in vector control.

Chikungunya Death Risk Factors in Brazil, in 2017: A case-control study.

de Moraes Alves Barbosa Oliveira, R., Kalline de Almeida Barreto, F., Praça Pinto, G., Timbó Queiroz, I., Montenegro de Carvalho Araújo, F., Wanderley Lopes, K., Lúcia Sousa do Vale, R., Rocha Queiroz Lemos, D., Washington Cavalcante, J., Machado Siqueira, A., Carla Vinhal Frutuoso, L., Carmen Duarte, E., Silva Lima Neto, A., Ricardo Ribas Freitas, A., Pamplona de Góes Cavalcanti, L.

07-04-2022

PLoS One

<https://doi.org/10.1371/journal.pone.0260939>

In 2016/2017 we had a major epidemic of chikungunya (CHIK) in Brazil, with many deaths. We evaluated to factors associated with deaths from CHIK that occurred in the city of Fortaleza, Brazil. A matched case-control study was conducted (1:2), by sex, age (\pm 5 years) and neighborhood. Cases were CHIK deaths that occurred between January 1 and December 31, 2017, in Fortaleza, Brazil, and which were laboratory confirmed. Controls were laboratory confirmed CHIK patients occurring in the same neighborhood and in the same period, but which did not progress to death. 82 cases of CHIK and 164 controls were included. Considering the clinical history, significant associations were found between other chronic heart diseases (OR 3.8; CI: 1.53-9.26) and chronic kidney disease (OR 12.77; CI: 2.75-59.4). In the multivariate analysis of the variables related to signs and symptoms, fever (OR: 19.23 CI: 1.73-213.78), abdominal pain (OR: 3; 74 CI: 1.06-13.16), apathy (OR: 11.62 CI: 2.95-45.82) and dyspnea (OR: 50.61; CI: 12.37-207.18) were identified with greater likelihood of death from CHIK. It also stood out that altered blood glucose was associated with cases with a worse prognosis (OR: 13.5; CI: 1.3-135.0). Among the laboratory findings, only lymphocytes and albumin were not associated

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with greater likelihood of death. The factors related with deaths were chronic kidney disease and previous heart disease, presence of fever, abdominal pain, apathy, dyspnea and arthritis and laboratory findings such as leukocytosis, leukopenia, thrombocytopenia, neutropenia and lymphopenia.

Fitness Cost of Sequential Selection with Deltamethrin in Aedes aegypti (Diptera: Culicidae).

Gonzalez-Santillan, F., Contreras-Perera, Y., Davila-Barboza, J., Juache-Villagrana, A., Gutierrez-Rodriguez, S., Ponce-Garcia, G., Lopez-Monroy, B., Rodriguez-Sanchez, I., Lenhart, A., Mackenzie-Impoinvil, L., Flores, A.

07-04-2022

J Med Entomol

<https://pubmed.ncbi.nlm.nih.gov/35389486>

In Mexico, *Aedes aegypti* (L.) is the primary dengue vector, chikungunya, and Zika viruses. The continued use of synthetic pyrethroids has led to the development of resistance in target populations, which has diminished the effectiveness of vector control programs. Resistance has been associated with disadvantages that affect the biological parameters of resistant mosquitoes compared to susceptible ones. In the present study, the disadvantages were evaluated by parameters related to survival and reproduction ('fitness cost') after selection with deltamethrin for five generations. The parameters analyzed were the length of the development cycle, sex ratio, survival, longevity, fecundity, egg viability, preoviposition, oviposition and postoviposition periods, and growth parameters. In the deltamethrin-selected strain, there was a decrease in the development cycle duration, the percentage of pupae, the oviposition period, and eggs viability. Although mean daily fecundity was not affected after the selection process, this, together with the decrease in the survival and fecundity levels by specific age, significantly affected the gross reproductive rate (GRR), net reproductive rate (Ro), and intrinsic growth rate (rm) of the group selected for five generations with deltamethrin compared to the group without selection. Identifying the 'cost' of resistance in biological fitness represents an advantage if it is desired to limit the spread of resistant populations since the fitness cost is the less likely that resistant individuals will spread in the population. This represents an important factor to consider in designing integrated vector management programs.

COVID-19 and Co-infections: A Serious Health Threat Requires Combination Diagnosis and Therapy.

Nawaz, S., Saleem, M.

06-04-2022

Infect Disord Drug Targets

<https://doi.org/10.2174/1871526522666220407001744>

Since the advent of the COVID-19 pandemic in 2019, a mammoth research activity targeting the etiological features of COVID-19 has commenced. Many aspects of the disease

have been studied, and various others are under consideration. The secondary microbial co-infections with COVID-19 have generated some serious concerns across the globe. This review mainly focuses on the notable secondary co-infections. The co-infection of influenza, tuberculosis, and typhoid may mimic the original COVID-19 symptoms. Physicians and clinicians must focus on the secondary co-infections which may aggravate the disease progression towards acute respiratory disorder syndrome (ARDS). Diagnostic strategies must also be redefined to determine the actual underlying secondary co-infection. There is a need for combination therapy and diagnostic approaches to minimize the risks associated with the COVID-19 pandemic effectively.

The compensatory reserve index predicts recurrent shock in patients with severe dengue.

Trieu, H., Khanh, L., Ming, D., Quang, C., Phan, T., Van, V., Deniz, E., Mulligan, J., Wills, B., Moulton, S., Yacoub, S.

07-04-2022

BMC Med

<https://doi.org/10.1186/s12916-022-02311-6>

Dengue shock syndrome (DSS) is one of the major clinical phenotypes of severe dengue. It is defined by significant plasma leak, leading to intravascular volume depletion and eventually cardiovascular collapse. The compensatory reserve Index (CRI) is a new physiological parameter, derived from feature analysis of the pulse arterial waveform that tracks real-time changes in central volume. We investigated the utility of CRI to predict recurrent shock in severe dengue patients admitted to the ICU. We performed a prospective observational study in the pediatric and adult intensive care units at the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam. Patients were monitored with hourly clinical parameters and vital signs, in addition to continuous recording of the arterial waveform using pulse oximetry. The waveform data was wirelessly transmitted to a laptop where it was synchronized with the patient's clinical data. One hundred three patients with suspected severe dengue were recruited to this study. Sixty-three patients had the minimum required dataset for analysis. Median age was 11 years (IQR 8-14 years). CRI had a negative correlation with heart rate and moderate negative association with blood pressure. CRI was found to predict recurrent shock within 12 h of being measured (OR 2.24, 95% CI 1.54-3.26), $P<0.001$. The median duration from CRI measurement to the first recurrent shock was 5.4 h (IQR 2.9-6.8). A CRI cutoff of 0.4 provided the best combination of sensitivity and specificity for predicting recurrent shock (0.66 [95% CI 0.47-0.85] and 0.86 [95% CI 0.80-0.92] respectively). CRI is a useful non-invasive method for monitoring intravascular volume status in patients with severe dengue.

Addressing the COVID-19 pandemic challenges for operational adaptations of a cluster randomized controlled trial on dengue vector control in Malaysia.

Saadatian-Elahi, M., Alexander, N., Möhlmann, T., Ariffin, F.,

Dengue, chikungunya et maladie à virus Zika

Schmitt, F., Richardson, J., Rabilloud, M., Hamid, N.

06-04-2022

BMC Public Health

<https://doi.org/10.1186/s12889-022-13026-x>

The COVID-19 pandemic placed an unprecedented overload on healthcare system globally. With all medical resources being dedicated to contain the spread of the disease, the pandemic may have impacted the burden of other infectious diseases such as dengue, particularly in countries endemic for dengue fever. Indeed, the co-occurrence of COVID-19 made dengue diagnosis challenging because of some shared clinical manifestations between the two pathogens. Furthermore, the sudden emergence and novelty of this global public health crisis has forced the suspension or slow-down of several research trials due to the lack of sufficient knowledge on how to handle the continuity of research trials during the pandemic. We report on challenges we have faced during the COVID-19 pandemic and measures that were implemented to continue the iDEM project (intervention for Dengue Epidemiology in Malaysia). This randomized controlled trial aims to assess the effectiveness of Integrated Vector Management (IVM) on the incidence of dengue in urban Malaysia by combining: targeted outdoor residual spraying (TORS), deployment of auto-dissemination devices (ADDs), and active community engagement (CE). Our operational activities started on February 10, 2020, a few weeks before the implementation of non-pharmaceutical interventions to contain the spread of COVID-19 in Malaysia. The three main issues affecting the continuity of the trial were: ensuring the safety of field workers during the interventions; ensuring the planned turnover of TORS application and ADD deployment and services; and maintaining the CE activities as far as possible. Even though the pandemic has created monumental challenges, we ensured the safety of field workers by providing complete personal protective equipment and regular COVID-19 testing. Albeit with delay, we maintained the planned interval time between TORS application and ADDs services by overlapping the intervention cycles instead of having them in a sequential scheme. CE activities continued remotely through several channels (e.g., phone calls and text messages). Sustained efforts of the management team, significant involvement of the Malaysian Ministry of Health and a quick and smart adaptation of the trial organisation according to the pandemic situation were the main factors that allowed the successful continuation of our research. Trial registration number: ISRCTN-81915073 . Date of registration: 17/04/2020, 'Retrospectively registered'.

Infectious diseases prevention and control using an integrated health big data system in China.

Zhou, X., Lee, E., Wang, X., Lin, L., Xuan, Z., Wu, D., Lin, H., Shen, P.

06-04-2022

BMC Infect Dis

<https://doi.org/10.1186/s12879-022-07316-3>

The Yinzhou Center for Disease Prevention and Control (CDC)

in China implemented an integrated health big data platform (IHBDP) that pooled health data from healthcare providers to combat the spread of infectious diseases, such as dengue fever and pulmonary tuberculosis (TB), and to identify gaps in vaccination uptake among migrant children. IHBDP is composed of medical data from clinics, electronic health records, residents' annual medical checkup and immunization records, as well as administrative data, such as student registries. We programmed IHBDP to automatically scan for and detect dengue and TB carriers, as well as identify migrant children with incomplete immunization according to a comprehensive set of screening criteria developed by public health and medical experts. We compared the effectiveness of the big data screening with existing traditional screening methods. IHBDP successfully identified six cases of dengue out of a pool of 3972 suspected cases, whereas the traditional method only identified four cases (which were also detected by IHBDP). For TB, IHBDP identified 288 suspected cases from a total of 43,521 university students, in which three cases were eventually confirmed to be TB carriers through subsequent follow up CT or T-SPOT.TB tests. As for immunization screenings, IHBDP identified 240 migrant children with incomplete immunization, but the traditional door-to-door screening method only identified 20 ones. Our study has demonstrated the effectiveness of using IHBDP to detect both acute and chronic infectious disease patients and identify children with incomplete immunization as compared to traditional screening methods.

Molecular and biological characterization of an Asian-American isolate of Chikungunya virus.

Archila, E., López, L., Castellanos, J., Calvo, E.

06-04-2022

PLoS One

<https://doi.org/10.1371/journal.pone.0266450>

Chikungunya virus is an arthropod-transmitted virus that causes chikungunya fever, a disease characterized by severe muscle and joint pain. In 2013, the virus was introduced to the Americas and caused approximately 2.7 million cases of infection during the subsequent two years. The lack of knowledge regarding the biological behavior of the viral strains circulating during the outbreak motivated the characterization of an isolate from the Colombian outbreak, starting from analysis of the complete genome to the biological behavior in vitro. The full genome was retrieved using next-generation sequencing. The infective and replicative capacities were evaluated in HEK293T, Huh-7, and MRC-5 cell lines. The infection rates were determined by flow cytometry, and the cytopathic effect was assessed by a resazurin fluorescent metabolic assay. The viral yield was quantified using the virus plaque formation assay, while the viral proteins and genomic RNA kinetics were subsequently evaluated by western-blot and RT-qPCR. The COL7624 isolate clustered with other American and Caribbean sequences in the Asian American lineage. The T669A substitution in E2 protein distinguished it from other Colombian sequences reported in 2014. After 48 h post infection (hpi), the three cell

lines analyzed reached infection percentages exceeding 65%, generating a high load of infectious viral progeny. The infection kinetics indicated that the replication peak of this CHIKV isolate is around 24 hpi, although gRNA is detectable in the culture supernatant from 4 hpi onwards. The infection caused the overexpression of interferon and pro-inflammatory cytokines, such as IL-1 β , TNF- α , and IL-8. The COL7624 CHIKV isolate exhibited a high infective and replicative capacity as well as activation of cellular immune responses, similar to isolates belonging to the other genotypes.

In silico and in vitro evaluation of silibinin: a promising anti-Chikungunya agent.

Dutta, S., Sengupta, S., Tripathi, A.

05-04-2022

In Vitro Cell Dev Biol Anim

<https://doi.org/10.1007/s11626-022-00666-x>

Chikungunya virus (CHIKV) infection and subsequent high patient morbidity is a global threat. The present study aimed to identify the potent antiviral agent against Chikungunya virus, with minimum in vitro cytotoxicity. CHIKV nsP4 3D structure was determined using the I-TASSER server followed by its refinement and pocket determination. Furthermore, high-throughput molecular docking was employed to identify candidate CHIKV nsP4 inhibitors in a library containing 214 compounds. The top ranked compound was evaluated further with various assays, including cytotoxicity, antiviral activity, time of drug addition, viral entry attachment, and microneutralization assays. High-throughput computational screening indicated silibinin to have the best interaction with CHIKV nsP4 protein, immature and mature glycoproteins with highest negative free binding energy, -5.24 to -5.86 kcal/mol, and the lowest inhibitory constant, 50.47 to 143.2 μ M. Further in vitro analysis demonstrated silibinin could exhibit statistically significant ($p < 0.05$) dose-dependent anti-CHIKV activity within 12.5-100- μ M concentrations with CC_{50} as 50.90 μ M. In total, 50 μ M silibinin interfered with both CHIKV attachment (75%) and entry (82%) to Vero cells. Time of addition assay revealed silibinin interfered with late phase of the CHIKV replication cycle. Microneutralization assay revealed that silibinin could inhibit clearing of 50% Vero cell monolayer caused by CHIKV-induced CPE at a minimum dose of 25 μ M. These data indicated silibinin to be a promising candidate drug against CHIKV infection.

RAGE

Molecular Basis of Functional Effects of Phosphorylation of the C-Terminal Domain of the Rabies Virus P Protein.

Zhan, J., Watts, E., Brice, A., Metcalfe, R., Rozario, A., Sethi, A., Yan, F., Bell, T., Griffin, M., Moseley, G., Gooley, P.

11-04-2022

J Virol

<https://doi.org/10.1128/jvi.00111-22>

The rabies virus (RABV) phosphoprotein (P protein) is expressed as several isoforms, which differ in nucleocytoplasmic localization and microtubule (MT) association, mediated by several sequences, including nuclear localization (NLS) and export (NES) sequences. This appears to underpin a functional diversity enabling multiple functions in viral replication and modulation of host biology. Mechanisms regulating trafficking are poorly defined, but phosphorylation by protein kinase C (PKC) in the P protein C-terminal domain (P_{CTD}) regulates nuclear trafficking, mediated by P_{CTD} -localized NLS/NES sequences, indicating that phosphorylation contributes to functional diversity. The molecular mechanism underlying the effects of PKC, and potential roles in regulating other host-cell interactions are unresolved. Here, we assess effects of phosphorylation on the P3 isoform, which differs from longer isoforms through an ability to localize to the nucleus and associate with MTs, which are associated with antagonism of interferon (IFN) signaling. We find that phosphomimetic mutation of the PKC site S210 inhibits nuclear accumulation and MT association/bundling. Structural analysis indicated that phosphomimetic mutation induces no significant structural change to the NLS/NES but results in the side chain of N226 switching its interactions from E228, within the NES, to E210. Intriguingly, N226 is the sole substituted residue between the P_{CTD} of the pathogenic IFN-resistant RABV strain Nishigahara and a derivative attenuated IFN-sensitive strain Ni-CE, inhibiting P3 nuclear localization and MT association. Thus, S210 phosphorylation appears to impact on N226/E228 to regulate P protein localization, with N226 mutation in Ni-CE mimicking a constitutively phosphorylated state resulting in IFN sensitivity and attenuation. **IMPORTANCE** Rabies virus P protein is a multifunctional protein with critical roles in replication and manipulation of host-cell processes, including subversion of immunity. This functional diversity involves interactions of several P protein isoforms with the cell nucleus and microtubules. Previous studies showed that phosphorylation of the P protein C-terminal domain (P_{CTD}) at S210, near nuclear trafficking sequences, regulates nucleocytoplasmic localization, indicating key roles in functional diversity. The molecular mechanisms of this regulation have remained unknown. Here, we show that phosphomimetic mutation of S210 regulates nuclear localization and MT association. This regulation does not appear to result from disrupted P_{CTD} structure, but rather from a switch of specific side chain interactions of N226. Intriguingly, N226 was previously implicated in P protein nuclear localization/MT association, immune evasion, and RABV pathogenesis, through undefined mechanisms. Our data indicate that the S210-N226 interface is a key regulator of virus-host interactions, which is significant for pathogenesis.

Single-cell reconstruction reveals input patterns and pathways into corticotropin-releasing factor neurons in the central amygdala in mice.

Huang, C., Wang, Y., Chen, P., Shan, Q., Wang, H., Ding, L., Bi, G., Zhou, J.
 06-04-2022
Commun Biol
<https://doi.org/10.1038/s42003-022-03260-9>

Corticotropin-releasing factor (CRF) neurons are one of the most densely distributed cell types in the central amygdala (CeA), and are involved in a wide range of behaviors including anxiety and learning. However, the fundamental input circuits and patterns of CeA-CRF neurons are still unclear. Here, we generate a monosynaptic-input map onto CeA-CRF neurons at single-cell resolution via a retrograde rabies-virus system. We find all inputs are located in 44 nested subregions that directly innervate CeA-CRF neurons; most of them are top-down convergent inputs expressing Ca^{2+} /calmodulin-dependent protein kinase II, and are centralized in cortex, especially in the layer 4 of the somatosensory cortex, which may directly relay information from the thalamus. While the bottom-up divergent inputs have the highest proportion of glutamate decarboxylase expression. Finally, en passant structures of single input neuron are revealed by in-situ reconstruction in a modified 3D-reference atlas, represented by a Periaqueductal gray-Subparafascicular nucleus-Subthalamic nucleus-Globus pallidus-Caudoputamen-CeA pathway. Taken together, our findings provide morphological and connectivity properties of inputs onto CeA-CRF neurons, which may provide insights for future studies interrogating circuit mechanisms of CeA-CRF neurons in mediating various functions.

Brain-wide mapping of inputs to the mouse lateral posterior (LP/Pulvinar) thalamus-anterior cingulate cortex network.

Leow, Y., Zhou, B., Sullivan, H., Barlowe, A., Wickersham, I., Sur, M.
 06-04-2022
J Comp Neurol
<https://doi.org/10.1002/cne.25317>

The rodent homolog of the primate pulvinar, the lateral posterior (LP) thalamus, is extensively interconnected with multiple cortical areas. While these cortical interactions can span the entire LP, subdivisions of the LP are characterized by differential connections with specific cortical regions. In particular, the medial LP has reciprocal connections with frontoparietal cortical areas, including the anterior cingulate cortex (ACC). The ACC plays an integral role in top-down sensory processing and attentional regulation, likely exerting some of these functions via the LP. However, little is known about how ACC and LP interact, and about the information potentially integrated in this reciprocal network. Here, we address this gap by employing a projection-specific monosynaptic rabies tracing strategy to delineate brain-wide inputs to bottom-up LP \rightarrow ACC and top-down ACC \rightarrow LP neurons. We find that LP \rightarrow ACC neurons receive inputs from widespread cortical regions, including primary and higher order sensory and motor cortical areas. LP \rightarrow ACC neurons also receive extensive subcortical inputs, particularly from the

intermediate and deep layers of the superior colliculus (SC). Sensory inputs to ACC \rightarrow LP neurons largely arise from visual cortical areas. In addition, ACC \rightarrow LP neurons integrate cross-hemispheric prefrontal cortex inputs as well as inputs from higher order medial cortex. Our brain-wide anatomical mapping of inputs to the reciprocal LP-ACC pathways provides a roadmap for understanding how LP and ACC communicate different sources of information to mediate attentional control and visuomotor functions.

TRACHOME

Community-level trachoma ecological associations and the use of geospatial analysis methods: A systematic review.

Burgert-Brucker, C., Adams, M., Mingkwan, P., Flueckiger, R., Ngondi, J., Solomon, A., Harding-Esch, E.
 08-04-2022
PLoS Negl Trop Dis
<https://doi.org/10.1371/journal.pntd.0010272>

Trachoma is targeted for global elimination as a public health problem by 2030. Understanding individual, household, or community-associated factors that may lead to continued transmission or risk of recrudescence in areas where elimination has previously been achieved, is essential in reaching and maintaining trachoma elimination. We aimed to identify climatic, demographic, environmental, infrastructural, and socioeconomic factors associated in the literature with trachoma at community-level and assess the strength of their association with trachoma. Because of the potential power of geospatial analysis to delineate the variables most strongly associated with differences in trachoma prevalence, we then looked in detail at geospatial analysis methods used in previous trachoma studies. We conducted a systematic literature review using five databases: Medline, Embase, Global Health, Dissertations & Theses Global, and Web of Science, including publications from January 1950 to January 2021. The review protocol was prospectively registered with PROSPERO (CRD42020191718). Of 35 eligible studies, 29 included 59 different trachoma-associated factors, with eight studies also including spatial analysis methods. Six studies included spatial analysis methods only. Higher trachomatous inflammation-follicular (TF) prevalence was associated with areas that: had lower mean annual precipitation, lower mean annual temperatures, and lower altitudes; were rural, were less accessible, had fewer medical services, had fewer schools; and had lower access to water and sanitation. Higher trachomatous trichiasis (TT) prevalence was associated with higher aridity index and increased distance to stable nightlights. Of the 14 studies that included spatial methods, 11 used exploratory spatial data analysis methods, three used interpolation methods, and seven used spatial modelling methods. Researchers and decision-makers should consider

Trachome

the inclusion and potential influence of trachoma-associated factors as part of both research activities and programmatic priorities. The use of geospatial methods in trachoma studies remains limited but offers the potential to define disease hotspots and areas of potential recrudescence to inform local, national, and global programmatic needs.

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.

07-04-2022

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 multi-component 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 hours 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 prior to RB-EB transitions in *C. trachomatis*-infected 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.

Characteristics and perspectives of patients with postoperative trichiasis in Hadiya Zone, Ethiopia.

Shrestha, R., Merbs, S., Bayissasse, B., Sisay, A., Beckwith, C., Courtright, P., Gower, E.

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Int Health

<https://doi.org/10.1093/inthealth/ihac004>

Postoperative trachomatous trichiasis (PTT) is a challenge for trichiasis surgery programs. Little is known about PTT patients' perceptions regarding outcomes and future disease management. This study aimed to understand the characteristics of PTT patients, how they managed trichiasis and their perceptions of prior surgeries and future surgery uptake. Patients with PTT were identified during an existing trichiasis screening program in Hadiya Zone, Ethiopia. A vision assessment and evaluation of the eyelids were conducted to determine distance vision, presence and severity of trichiasis

and eyelid contour abnormalities. A questionnaire was administered to obtain information regarding patients' perceptions of surgery and PTT management approaches. Descriptive statistics were used to characterize PTT and determine associations between PTT severity and patient perceptions. Among 404 participants, most were female (79.7%) and aged 40-60 y (62.6%). In total, 514 eyelids had PTT, and nearly half had severe PTT (46.9%). Although >50% of participants were currently epilating to manage their PTT, the majority (82.8%) indicated that they wanted repeat surgery. Most participants indicated that pain persisted despite epilation. The majority (75.1%) indicated satisfaction with their prior surgery and 59.6% indicated that they would recommend surgery to others. This study, which included a large proportion of severe PTT cases, indicated that individuals were generally satisfied with prior surgery and would prefer to have surgery again for PTT management.

Productivity, efficiency and gender equity of community mobilisation approaches in trichiasis campaigns: analysis of programmatic data from seven sub-Saharan African countries.

UI Hassan, E., Kelly, M., Waititu, T., Olobio, N., Kabona, G., Mkocha, H., Kivumbi, P., Mwale, C., Mubangizi, A., Mugume, F., Baayenda, G., Mayeku, R., Massangaie, M., Mbofana, M., Cumaio, M., Sisay, A., Mersha, T., Courtright, P.

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Int Health

<https://doi.org/10.1093/inthealth/ihab086>

Achieving elimination of trachoma as a public health problem in trichiasis-endemic districts requires a systematic approach to trichiasis case finding and outreach. Programme monitoring data from seven countries for 2017-2019 were used to explore the efficiency of different community mobilisation approaches and uptake of trichiasis surgical services. Three countries (Ethiopia, Kenya and Mozambique) using broad-based community mobilisation strategies had large numbers of people presenting at outreach but only 2.9% of them had trichiasis, while in four countries (Nigeria, Tanzania, Uganda and Zambia) using house-to-house case finding, 37.5% of outreach attendees had trichiasis. Countries using house-to-house case finding have proportionally more women attending outreach compared with countries using broad-based mobilisation. Among trichiasis cases offered surgery 86% accepted, which was similar for men and women. In these settings, house-to-house case finding appears to be a more effective and efficient approach to ensure that trichiasis cases, particularly in women, obtain access to surgical services.

ULCERE DE BURULI

Mycobacterium ulcerans Experimental Dormancy.

Loukil, A., Lalaoui, R., Bogreau, H., Regoui, S., Drancourt, M., Hammoudi, N.

11-04-2022

Am J Trop Med Hyg

<https://doi.org/10.4269/ajtmh.21-1327>

Whether *Mycobacterium ulcerans*, the etiological agent of Buruli ulcer in numerous tropical countries, would exist in a dormant state as reported for closely related *Mycobacterium* species, has not been established. Six *M. ulcerans* strains were exposed to a progressive depletion in oxygen for 2 months, using the Wayne model of dormancy previously described for *M. tuberculosis*, and further examined by microscopy after staining of dynamic, dormant, and dead mycobacteria (DDD staining), microcalorimetry and subculture in the presence of dead and replicative *M. ulcerans* as controls. *Mycobacterium ulcerans* CU001 strain died during the progressive oxygen depletion and four of five remaining strains exhibited Nile red-stained intracellular lipid droplets and a 14- to 20-day regrowth when exposed to ambient air, consistent with dormancy. A fifth *M. ulcerans* 19423 strain stained negative in DDD staining and slowly regrew in 27 days. Three tested *M. ulcerans* strains yielded microcalorimetric pattern similar to that of the negative (dead) homologous controls, differing from that of the homologous positive (replicative) controls. The relevance of these experimental observations, suggesting a previously unreported dormancy state of *M. ulcerans*, warrants further investigations in the natural ecological niches where *M. ulcerans* thrive as well as in Buruli ulcer lesions.

as a public health problem. This systematic review aims to evaluate the accuracy of rapid point-of-care (POC) tests for diagnosis of leprosy. Searches were carried out in electronic databases (PubMed, EMBASE, CRD, Cochrane Library and LILACS) in April 2021 for patients with suspicion or confirmatory diagnostic of leprosy, classified in multibacillary (MB) or paucibacillary (PB) cases, performing rapid POC serological tests compared to clinical evaluation, smear microscopy and immunohistochemistry analysis. Methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2). A meta-analysis was undertaken to generate pooled estimates of diagnostic parameters, presenting sensitivity, specificity and diagnostic odds ratio (DOR) values. The review protocol was registered at PROSPERO, CRD # 42014009658. From 893 potentially relevant references, 12 articles were included reporting 16 diagnostic tests accuracy studies with 5395 individuals enrolled. Meta-analysis of NDO-LID and PGL-I tests data in MB patients showed sensitivity and specificity [95% confidence interval (CI)] of 0.83 (0.71-0.91), 0.91 (0.72-0.97); and 0.92 (0.86-0.96), 0.93 (0.78-0.98); respectively, with high heterogeneity among the studies. Our results can inform policymakers regarding the possibility of implementing accurate, rapid POC tests for leprosy in public health services, especially within primary health care.

Asymmetrical ocular affliction in a case of recurrent erythema nodosum leprosum-an uncommon manifestation of leprosy in contemporary times.

Sachdeva, S., Sardana, K., Kumari, R., Bhogar, K., Khurana, A., Malhotra, P.

11-04-2022

Int J Dermatol

<https://doi.org/10.1111/ijd.16195>

PIAN

LEPRE

Accuracy of rapid point-of-care serological tests for leprosy diagnosis: a systematic review and meta-analysis.

Romero, C., Castro, R., do Brasil, P., Pereira, D., Pinheiro, R., Toscano, C., de Oliveira, M.

08-04-2022

Mem Inst Oswaldo Cruz

<https://pubmed.ncbi.nlm.nih.gov/35416839>

Leprosy is a chronic infectious disease, still endemic in many countries that may lead to neurological, ophthalmic, and motor sequelae if not treated early. Access to timely diagnosis and multidrug therapy (MDT) remains a crucial element in the World Health Organization's strategy to eliminate the disease

Different cell death mechanisms are involved in leprosy pathogenesis.

Rodrigues de Sousa, J., Magno Falcão, L., Virgolino, G., Santos Cruz, M., Teixeira, V., Leila de Souza Aarão, T., Furlaneto, I., Oliveira Carneiro, F., Amin, G., Fuzii, H., Simões Quaresma, J.

06-04-2022

Microb Pathog

<https://pubmed.ncbi.nlm.nih.gov/35398215>

Leprosy is a chronic granulomatous disease that remains a serious public health problem in developing countries. According to the Madrid classification, leprosy presents in four clinical forms: two immunologically unstable forms (indeterminate and borderline) and two stable polar forms (tuberculoid and lepromatosus). In leprosy, the relationship of cell death to clinical disease outcome remains unclear. Therefore, we investigated the extent of autophagy and different cell death mechanisms-such as apoptosis, necroptosis, and pyroptosis-in cutaneous lesions of patients with leprosy, as well as the role of these mechanisms in clinical disease progression. This cross-sectional analytical

Trypanosomes (trypanosomiase et maladie de Chagas)

study included 30 patients with a confirmed diagnosis of leprosy, with 10 patients in each of the following groups: lepromatous (LL), tuberculoid (TT), and indeterminate (II) leprosy groups. For histopathological analysis, skin samples were subjected to haematoxylin-eosin staining and immunostaining for apoptotic and necroptotic markers. The results indicated that FasL expression was much higher in the LL form than in the TT and II forms. Similar results (higher expression in the LL form than in the TT and II forms) were observed for caspase 8, RIP1, and RIP3 expressions. MLKL, BAX, and caspase 3 expression levels were highest in the LL form, especially in globular foamy macrophages. Beclin-1 expression was highest in the TT form but was low in LL and II forms. Caspase 1 expression was highest in the LL form, followed by that in the TT and II forms. In conclusion, our study elucidates the role of different cell death mechanisms in the pathophysiology of various forms of leprosy and suggests measures that may be used to control the host response to infection and disease progression.

The life experience of leprosy families in maintaining interaction patterns in the family to support healing in leprosy patients in Indonesian society. A phenomenological qualitative study.

Nasir, A., Yusuf, A., Listiawan, M., Makhfudli, M.

08-04-2022

PLoS Negl Trop Dis

<https://doi.org/10.1371/journal.pntd.0010264>

Family involvement in overcoming the severity of leprosy is very important in the life of leprosy sufferers in communities who experience the clinical and, psychological, social and behavioral consequences of the disease. However, this need, psychosocial, is felt to be not optimal. This study is to identify how the experiences of family members as caregivers provide assistance to lepers in improving healing and maintaining patterns of interaction in the family. The design uses qualitative research with in-depth, face-to-face interviews with family members in a semi-structured manner with the hope of obtaining complete data. Using purposive sampling with Participatory Interpretative Phenomenology analysis, there are 12 families with 15 family members consisting of 4 men and 11 women. This study produced a family theme that tried to follow what would happen to lepers, with four sub-categories: 1) Using various coping alternatives to recognize the disease, 2) Family members in the shadow of leprosy, 3) Trying to empathize with other family members. sick, 4) Caring for the emotional response of the family and seeking support. This analysis shows that deficiency in cognitive aspects can be closed by maintaining a lifestyle in the family through efforts to understand, support, establish communication, increase maximum involvement in restoring self-confidence, especially in lepers with psychosocial problems in the family. The results of this study can be used as psychosocial support in maintaining communication between family members to support treatment programs and accelerate the recovery of leprosy.

TRYPANOSOMES (TRYPANOSOMIASE ET MALADIE DE CHAGAS)

Letters to the Editor: Indeterminate form of Chagas Disease: some immunological insights.

Hasslocher-Moreno, A., Xavier, S., Saraiva, R., Sousa, A.

08-04-2022

Rev Soc Bras Med Trop

<https://pubmed.ncbi.nlm.nih.gov/35416886>

Prevalence of Chagas Disease and Associated Factors in an Endemic Area of Northeastern Argentina.

Baeck, M., Mando, P., Virasoro, B., Martinez, A., Zarate, S., Valentini, R., Lopez Saubidet, I.

11-04-2022

Am J Trop Med Hyg

<https://doi.org/10.4269/ajtmh.21-0646>

Chagas disease caused by *Trypanosoma cruzi*, remains one of the leading public health problems in Latin America. The number of infections in nonendemic countries continues to rise as a consequence of migratory flows. Updated information on prevalence, especially in treatable stages, together with vector eradication programs are key factors in an attempt to control the disease. We aim to estimate the prevalence of *T. cruzi* infection in an endemic area of Argentina and to describe epidemiological and clinical factors related to the disease. This is a cross-sectional study in an endemic rural area of Argentina. Our target population was people between 10 and 20 years of age, collecting demographic, clinical, and electrocardiographic data and seroprevalence against *T. cruzi*. We included 460 subjects; 76.7% did not have drinking water; 49.3% reported the presence of *Triatoma infestans* at home; 79.1% had pets or birds; 72.6% lived close to a chicken coop; 24.6% lived in adobe houses; 27.8% lived in overcrowded conditions. Seroprevalence was 9.33%. In the multivariate analysis, the presence of *Triatoma infestans* at home (OR 2.08, P = 0.03) had an association with seropositivity. No relevant findings indicating acute or chronic organ involvement were detected. We found no correlation of right bundle branch block (RBBB) and Chagas disease in our population. None of the infected patients were previously aware of their condition, highlighting the importance of active surveillance to detect infection in a potentially treatable stage, especially in areas with difficult access to health programs.

Acute Chagas Disease Caused by *Trypanosoma cruzi* TcIV and Transmitted by *Panstrongylus geniculatus*: Molecular Epidemiological Insights Provided by the First Documented Autochthonous Case in Rondônia, Southwestern Amazonia, Brazil.

Julião, G., Bragança, M., Torres, P., Lima, L., Neves, R., Nobre, J., Vergara-Meza, J., Basano, S., Moraes, F., Baldez, M., Tada, M.,

Trypanosomes (*trypanosomiase et maladie de Chagas*)

Lima, A., Costa, J., Gil, L., Cunha, A., Camargo, E., Teixeira, M.

11-04-2022

Vector Borne Zoonotic Dis

<https://doi.org/10.1089/vbz.2021.0086>

Recurrent outbreaks of oral infection and isolated cases characterize the new epidemiological scenario of Chagas disease (CD) in the Brazilian Amazon. Acute Chagas disease (ACD) is common in Pará and Amazonas, Northeastern and Northwestern Brazilian Amazonia. In the present study, we describe the first molecularly characterized autochthonous case of ACD in Rondônia, Southwestern Amazonia. The patient, a 39-year-old male resident in the small city of Cujubim, presented typical ACD symptoms: fever, asthenia, myalgia, progressive dyspnea, swelling of the legs, and tiredness at minimal efforts, all compatible with ACD and indicative of cardiac involvement. A thick blood drop test revealed trypomastigote forms of *Trypanosoma cruzi* genotyped as TcIV. An epidemiological investigation ruled out oral infection, and support for vectorial transmission included the finding of *Panstrongylus geniculatus* positive for *T. cruzi* (TcIII and TcIV) inside the tent used by the patient when harvesting forest timber, and a circular cutaneous lesion resembling a chagoma of inoculation. Treatment with benznidazole led to blood parasite clearance as confirmed by molecular tests. Altogether, our findings fitted well into the ecological scenario where deforestation and colonization of forested areas represent an important risk factor to the adaptation of *P. geniculatus* to human habitats, favoring vectorial transmission of CD in the Amazonian region.

Approaches to advance drug discovery for neglected tropical diseases.

Revue de littérature

Ferreira, L., de Moraes, J., Andricopulo, A.

07-04-2022

Drug Discov Today

<https://pubmed.ncbi.nlm.nih.gov/35398562>

Neglected tropical diseases (NTDs), which include leishmaniasis, Chagas disease, human African trypanosomiasis (HAT), and schistosomiasis, remain public health problems in developing countries, as highlighted in the 2021-2030 WHO Roadmap on NTDs. This agenda sets the challenges for the control and elimination of NTDs by 2030. Fortunately, NTD drug discovery has shifted from traditional to modern strategies combining medicinal chemistry, phenotypic and molecular assays, multiparameter optimization, structural biology, and 'omics approaches. Structure- and ligand-based drug design have fostered NTD drug discovery by enabling data-driven molecular optimization, expansion to previously inaccessible chemical spaces, and knowledge building from biological data. These efforts have integrated parasite biology and medicinal chemistry to advance drug discovery in this key area of global health. Teaser: Novel knowledge on parasite biology and medicinal chemistry has been key to advancing structure- and ligand-based NTD drug discovery.

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

Bobba, V., Li, Y., Afrin, M., Dano, R., Zhang, W., Li, B., Su, B.

04-04-2022

Bioorg Med Chem

<https://pubmed.ncbi.nlm.nih.gov/35396128>

Human African trypanosomiasis is caused by a protozoan parasite *Trypanosoma brucei* majorly infecting people living in sub-Saharan Africa. Current limited available treatments suffer from drug resistance, severe adverse effects, low efficacy, and costly administrative procedures in African countries with limited medical resources. Therefore, there is always a perpetual demand for advanced drug development and invention of new strategies to combat the disease. Previous work in our lab generated a library of sulfonamide analogs as selective tubulin inhibitors, based on the structural difference between mammalian and trypanosome tubulin proteins. Further lead derivatization was performed in the current study and generated 25 potential drug candidates to improve the drug efficacy and uptake by selectively targeting the parasite's P2 membrane transporter protein with imidamide moiety. One of the newly synthesized analogs, compound 25 with a di-imidamide moiety, has shown greater potency with an IC₅₀ of 1 nM to selectively inhibit the growth of trypanosome cells without affecting the viability of mammalian cells. Western blot analyses reveal that the compound suppressed tubulin polymerization in *T. brucei* cells. A detailed structure-activity relationship (SAR) was summarized that will be used to guide future lead optimization.

Emergence of Congenital Chagas Disease in Ireland.

Stone, R., Gavin, P., Chiodini, P., Nolder, D., McGettrick, P., Keogh, A., Mc Entagart, N., Drew, R., Lambert, J., Ferguson, W.

06-04-2022

Pediatr Infect Dis J

<https://doi.org/10.1097/INF.0000000000003546>

Chagas disease (CD) is an under-diagnosed tropical disease that is increasingly being observed outside of Latin America. We describe the first 2 infants with congenital Chagas Disease (cCD) in Ireland. Clinicians in nonendemic countries need to be aware of the potential for cCD due to the migration of women from countries of high prevalence.

Antiparasitic treatment with itraconazole and amiodarone in 2 dogs with severe, symptomatic Chagas cardiomyopathy.

Malcolm, E., Saunders, A., Vitt, J., Boutet, B., Hamer, S.

07-04-2022

J Vet Intern Med

<https://doi.org/10.1111/jvim.16422>

Chagas cardiomyopathy, caused by the protozoal parasite *Trypanosoma cruzi*, is characterized by arrhythmias, myocardial damage, heart failure, and sudden death. We describe 2 dogs with severe, symptomatic Chagas cardiomyopathy characterized by myocardial dysfunction and

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electrocardiographic abnormalities that were managed with a combination of cardiac medications and antiparasitic treatment with itraconazole and amiodarone. Both dogs died suddenly within 6 months of diagnosis. These cases highlight the need for early detection of Chagas disease in dogs and continued research to develop effective antiparasitic treatment protocols.

Total Synthesis and Structure Correction of the Cyclic Lipodepsipeptide Orfamide A.

Bando, Y., Hou, Y., Seyfarth, L., Probst, J., Götze, S., Bogacz, M., Hellmich, U., Stallforth, P., Mittag, M., Arndt, H.

09-03-2022

Chemistry

<https://doi.org/10.1002/chem.202104417>

A total synthesis of the cyclic lipodepsipeptide natural product orfamide A was achieved. By developing a synthesis format using an aminoacid ester building block and SPPS protocol adaptation, a focused library of target compounds was obtained, in high yield and purity. Spectral and LC-HRMS data of all library members with the isolated natural product identified the ⁵ Leu residue to be d- and the 3'-OH group to be R-configured. The structural correction of orfamide A by chemical synthesis and analysis was confirmed by biological activity comparison in *Chlamydomonas reinhardtii*, which indicated compound configuration to be important for bioactivity. Acute toxicity was also found against *Trypanosoma brucei*, the parasite causing African sleeping sickness.

LEISHMANIOSE

Exploring IL-17 gene promoter polymorphisms in canine leishmaniasis.

Gonçalves-de-Albuquerque, S., da Silva, L., de Sousa-Paula, L., Sales, K., Boegel, A., Dantas-Torres, F.

11-04-2022

Acta Trop

<https://pubmed.ncbi.nlm.nih.gov/35421384>

Proinflammatory cytokine secretion determines the infection course in leishmaniasis. The immunopathology of canine leishmaniasis (CanL) caused by *Leishmania infantum* is characterized by low *Leishmania*-specific IFN- γ and IL-17 production. Mutations in the human IL-17 gene promoter alter cytokine expression and may increase the susceptibility of humans to some infectious diseases. In this study, we correlated canine IL-17 single nucleotide polymorphisms (SNPs) with anti-*Leishmania* IgG levels, parasite load and external clinical signs in dogs naturally exposed to *L. infantum* in Brazil. A higher frequency (Chi-square test: $X^2= 5.378$, df= 1, P= 0.020) of major alleles was observed among dogs showing no external clinical signs attributable to *Leishmania* infection. A high proportion of A allele carriers (mutant) were observed

among dogs with high antibody levels, although differences were not statistically significant (Chi-square test: $X^2= 4.410$, df= 4, P= 0.353), as compared to dogs with low antibody levels. In general, the association of canine IL-17 SNPs with disease expression or disease exacerbation did not reach enough statistical power to allow the use of these mutations as prognostic markers. This knowledge may pave the way for further investigations on the genetic aspects of CanL and its immunotherapy.

In vitro and in vivo Anti-leishmanial Potential of [Ag(PTA)4]BF4 and [Ag(HBPz3)(PPh3)] Silver Complexes.

Soldera, P., Chagas, A., Brasil, A., Comandolli-Wyrepkowski, C., Porchia, M., Pereira, A.

08-04-2022

Rev Soc Bras Med Trop

<https://pubmed.ncbi.nlm.nih.gov/35416873>

American tegumentary leishmaniasis is a parasitic disease known for being difficult to treat; therefore, the search for more effective therapeutic methods is necessary. The objective of this study was to evaluate the in vitro and in vivo antileishmanial activity of silver complexes [Ag(PTA)4]BF4 (Ag1) and [Ag(HBPz3)(PPh3)] (Ag2) against *Leishmania (Leishmania) amazonensis* [*L. (L.) amazonensis*] and *Leishmania (Viannia) guyanensis*. In vitro bioassays were performed to evaluate the activity of the complexes against promastigote and amastigote forms and evaluate their cytotoxicity. In vivo experiments were performed with hamsters (*Mesocricetus auratus*) infected and treated topically with two gels containing each metallic complex. Both complexes reduced the number of viable parasites against the promastigote forms of *L. (L.) amazonensis*. Ag2 was mainly effective against the amastigote forms. The Ag2 complex did not present cellular cytotoxicity, and regarding the selectivity index, both complexes were considered acceptable, with Ag2 having the best selectivity index in murine peritoneal macrophages in relation to *L. (L.) amazonensis*. Ag2 showed better results in the topical treatment against infections caused by *L. (L.) amazonensis*, with a small reduction in the lesion volume after the 14th day of treatment and less parasitic load at the lesion site. Ag2 was more effective than Ag1 against *L. (L.) amazonensis*.

Dogs with leishmaniosis: how are we managing proteinuria in daily practice? A Portuguese questionnaire-based study.

Monteiro, M., Prata, S., Cardoso, L., Pereira da Fonseca, I., Leal, R.

11-04-2022

Parasit Vectors

<https://doi.org/10.1186/s13071-022-05222-w>

Proteinuria is a common finding in dogs with leishmaniosis. Although antileishmanial therapeutic protocols are widely implemented, little information is available on which

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treatments are most adequate for identifying proteinuria in patients with canine leishmaniosis (CanL), especially regarding the use of immunosuppressants. The aim of this study was to explore the current paradigm regarding the antiproteinuric approach adopted by veterinary practitioners in Portugal to treat dogs with CanL. A questionnaire-based study was developed using Google Forms®. The questionnaire presented a number of different hypothetical scenarios of CanL, and the topics surveyed included the general features of the respondents and the protocols preferred by these respondents to manage proteinuria in the presented scenarios, including choice of therapeutic drugs, appropriate diet and use of immunosuppressants, in dogs with immune-mediated glomerulonephritis. The questionnaire was internally prevalidated and diffused online over a 2-month period through Portuguese veterinary social networking groups, and data were collected for descriptive analysis. A total of 86 veterinary practitioners responded to the survey. When exposed to theoretical scenarios of proteinuria in dogs with CanL at stages IIb, III and IV (LeishVet guidelines), 16.3%, 62.8% and 93.8% of the respondents, respectively, answered that they would treat it. The dog was started on a renal diet as therapy by 28.6%, 83.3% and 97.4% of respondents, respectively. Angiotensin-converting enzyme inhibitors (ACEI) were prescribed by 100%, 85.2% and 78.9% of respondents as first-choice drugs for CanL at stages IIb, III and IV, respectively, with ACEI used in monotherapy by 64.3%, 40.7% and 46.1%. In comparison, protocols using ACEI in combination with other compounds were chosen by 7.1%, 33.3% and 39.5% of respondents, and combination therapy which did not include ACEI was the choice of 0.0%, 12.9% and 14.5%. Regarding immunosuppressants, 44.2% of the respondents answered they would prescribe them, with 97.4% electing for prednisolone and 5.3% choosing mycophenolate mofetil. Among the veterinary practitioners who responded, proteinuria treatment was considered since stage IIb CanL, although implementation of a therapeutic approach was more evident in advanced CanL stages. ACEI were the first-choice drugs, particularly for the treatment of stage IIb CanL; in advanced stages, a combination of antiproteinuric drugs was more often used. Immunosuppressant use was controversial, although when applied, prednisolone was the preferred choice. These findings reinforce the small body of evidence that supports the use of such drugs and the need to further explore their role in CanL.

Responsible companion animal guardianship is associated with canine visceral leishmaniasis: an analytical cross-sectional survey in an urban area of southeastern Brazil.

Soares, P., da Silva, E., Penaforte, K., Ribeiro, R., de Melo, M., Cardoso, D., Santos, I., Machado, R., Trindade, C., Cunha, A., Teixeira-Neto, R., de Melo, S., de Aquino, V., Belo, V.

11-04-2022

BMC Vet Res

<https://doi.org/10.1186/s12917-022-03238-z>

Responsible companion animal guardianship (RCAG)

comprises a set of concepts involving activities, behavior and care that guardians must provide to ensure the welfare of their animals. When such principles are disregarded, the risk of animals developing zoonotic diseases, such as canine visceral leishmaniasis (CVL), increases. This disease is a public health problem in many urban settings in Brazil because dogs are the main reservoirs of Leishmania and are involved in the transmission of the parasites to humans. Our analytical cross-sectional epidemiological survey aimed to investigate the prevalence of CVL in a city in southeastern Brazil and to establish the association between the disease and a number of predictor variables including dog traits, socioeconomic status of guardians, ecological features of the domicile and RCAG. Our study showed that the global prevalence of CVL in the sample canine population was 6.7% (47/704). All variables related to better dog care were associated with lower chances of infection. Multiple regression analysis revealed that the chances of animals being seropositive for CVL were significantly ($p<0.05$) higher when guardians had no formal education or possessed a university degree (vs. those with complete primary or secondary schooling) and when dogs were sheltered outside the house and had free access to the streets. An additional novel finding was that dogs that were acquired as puppies presented half of the chance of developing the disease in comparison with those acquired at the adult stage. Geographically weighted logistic regression coefficients showed that the strengths of the predictor/CVL associations varied depending on the studied geographical space. Both models demonstrated that the associations were always in the same directions. Our findings indicate that regardless of age and mode of acquisition, adult dogs should be submitted to clinical evaluation and tests for CVL. RCAG can exert positive effects on the control of CVL.

Determination of the trend of incidence of cutaneous leishmaniasis in Kerman province 2014-2020 and forecasting until 2023. A time series study.

Afshar, P., Bahrampour, A., Shahesmaeli, A.

11-04-2022

PLoS Negl Trop Dis

<https://doi.org/10.1371/journal.pntd.0010250>

Cutaneous leishmaniasis (CL) is currently a health problem in several parts of Iran, particularly Kerman. This study was conducted to determine the incidence and trend of CL in Kerman during 2014-2020 and its forecast up to 2023. The effects of meteorological variables on incidence was also evaluated. 4993 definite cases of CL recorded from January 2014 to December 2020 by the Vice-Chancellor for Health at Kerman University of Medical Sciences were entered. Meteorological variables were obtained from the national meteorological site. The time series SARIMA methods were used to evaluate the effects of meteorological variables on CL. Monthly rainfall at the lag 0 ($\beta = -0.507$, 95% confidence interval:-0.955,-0.058) and monthly sunny hours at the lag 0 ($\beta = -0.214$, 95% confidence interval:-0.308,-0.119) negatively associated with the incidence of CL. Based on the Akaike

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information criterion (AIC) the multivariable model (AIC = 613) was more suitable than univariable model (AIC = 690.66) to estimate the trend and forecast the incidence up to 36 months. The decreasing pattern of CL in Kerman province highlights the success of preventive, diagnostic and therapeutic interventions during the recent years. However, due to endemicity of disease, extension and continuation of such interventions especially before and during the time periods with higher incidence is essential.

Harnessing Fuzzy Rule Based System for Screening Major Histocompatibility Complex Class I Peptide Epitopes from the Whole Proteome: An Implementation on the Proteome of *Leishmania donovani*.

Vijayakumar, S.

11-04-2022

J Comput Biol

<https://doi.org/10.1089/cmb.2021.0464>

The development of peptide-based vaccines is enhanced by immunoinformatics, which predicts the patterns that B cells and T cells recognize. Although several tools are available for predicting the Major histocompatibility complex (MHC-I) binding peptides, the wide variants of human leucocyte antigen allele make it challenging to choose a peptide that will induce an immune response in a majority of people. In addition, for a peptide to be considered a potential vaccine candidate, factors such as T cell affinity, proteasome cleavage, and similarity to human proteins also play a major role. Identifying peptides that satisfy the earlier cited measures across the entire proteome is, therefore, challenging. Hence, the fuzzy inference system (FIS) is proposed to detect each peptide's potential as a vaccine candidate and assign it either a very high, high, moderate, or low ranking. The FIS includes input features from 6 modules (binding of 27 major alleles, T cell propensity, pro-inflammatory response, proteasome cleavage, transporter associated with antigen processing, and similarity with human peptide) and rules derived from an observation of features on positive samples. On validation of experimentally verified peptides, a balanced accuracy of ~80% was achieved, with a Mathew's correlation coefficient score of 0.67 and an F-1 score of 0.74. In addition, the method was implemented on complete proteome of *Leishmania donovani*, which contains ~4,800,000 peptides. Lastly, a searchable database of the ranked results of the *L. donovani* proteome was made and is available online (MHC-FIS-LdDB). It is hoped that this method will simplify the identification of potential MHC-I binding candidates from a large proteome.

Approaches to advance drug discovery for neglected tropical diseases.

Revue de littérature

Ferreira, L., de Moraes, J., Andricopulo, A.

07-04-2022

Drug Discov Today

<https://pubmed.ncbi.nlm.nih.gov/35398562>

Neglected tropical diseases (NTDs), which include leishmaniasis, Chagas disease, human African trypanosomiasis (HAT), and schistosomiasis, remain public health problems in developing countries, as highlighted in the 2021-2030 WHO Roadmap on NTDs. This agenda sets the challenges for the control and elimination of NTDs by 2030. Fortunately, NTD drug discovery has shifted from traditional to modern strategies combining medicinal chemistry, phenotypic and molecular assays, multiparameter optimization, structural biology, and 'omics approaches. Structure- and ligand-based drug design have fostered NTD drug discovery by enabling data-driven molecular optimization, expansion to previously inaccessible chemical spaces, and knowledge building from biological data. These efforts have integrated parasite biology and medicinal chemistry to advance drug discovery in this key area of global health. Teaser: Novel knowledge on parasite biology and medicinal chemistry has been key to advancing structure- and ligand-based NTD drug discovery.

Antileishmanial activity of Riparin structural analogs of *Aniba riparia*: Biological evaluation, in silico Adme-Tox, and molecular docking.

Figueiredo, K., Magalhães Costa, R., Rocha, J., Chavez Gutierrez, S., Ramos, R., Muálem de Moraes Alves, M., Aécio de Amorim Carvalho, F., Menezes Carvalho, A., Lima, F.

06-04-2022

Exp Parasitol

<https://pubmed.ncbi.nlm.nih.gov/35398101>

We performed a biological evaluation of antileishmanial activity, in silico ADME-Tox profile, and molecular docking of riparins A-F. The antileishmanial activity was evaluated in Leishmania major promastigotes, whereas the cytotoxic activity was tested on murine macrophages. Computational parameters were predicted by in silico analysis. Molecular docking was performed with 18 *L. major* molecular targets. Riparins, especially RipC and RipE, showed cytotoxic activity in vitro toward *L. major* promastigotes and a high selectivity index. Riparins showed small differences in their physicochemical properties, such as polarity and aqueous solubility. LogP was an important parameter for the differences in the antileishmanial activity between the molecules. In molecular docking, the ligands displayed $K_i < 1 \mu\text{M}$ for LmNMT and LmLEI. Significant molecular interactions were observed with residues from the active site and adjacent regions of such enzymes. Thus, riparins have the potential for application in antileishmanial therapy.

Ligand-induced structural transitions combined with paramagnetic ions facilitate unambiguous NMR assignments of methyl groups in large proteins.

Mühlberg, L., Alarcin, T., Maass, T., Creutznacher, R., Küchler, R., Mallagaray, A.

10-04-2022

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J Biomol NMR
<https://doi.org/10.1007/s10858-022-00394-0>

NMR spectroscopy allows the study of biomolecules in close-to-native conditions. Structural information can be inferred from the NMR spectra when an assignment is available. Protein assignment is usually a time-consuming task, being specially challenging in the case of large, supramolecular systems. Here, we present an extension of existing state-of-the-art strategies for methyl group assignment that partially overcomes signal overlapping and other difficulties associated to isolated methyl groups. Our approach exploits the ability of proteins to populate two or more conformational states, allowing for unique NOE restraints in each protein conformer. The method is compatible with automated assignment algorithms, granting assignments beyond the limits of a single protein state. The approach also benefits from long-range structural restraints obtained from metal-induced pseudocontact shifts (PCS) and paramagnetic relaxation enhancements (PREs). We illustrate the method with the complete assignment of the ¹⁹⁹ methyl groups of a MIL^{proS}V^{proS}AT methyl-labeled sample of the UDP-glucose pyrophosphorylase enzyme from Leishmania major (LmUGP). Protozoan parasites of the genus Leishmania causes Leishmaniasis, a neglected disease affecting over 12 million people worldwide. LmUGP is responsible for the de novo biosynthesis of uridine diphosphate-glucose, a precursor in the biosynthesis of the dense surface glycocalyx involved in parasite survival and infectivity. NMR experiments with LmUGP and related enzymes have the potential to unravel new insights in the host resistance mechanisms used by Leishmania major. Our efforts will help in the development of selective and efficient drugs against Leishmania.

Gold and silver nanoparticles functionalized with 4',7-dihydroxyflavone exhibits activity against Leishmania donovani.

Sasidharan, S., Saudagar, P.

05-04-2022

Acta Trop

<https://pubmed.ncbi.nlm.nih.gov/35395228>

Leishmaniasis is a neglected tropical disease that has been burdening the world for over a century. Though there are drugs to treat leishmaniasis, the repertoire suffers several drawbacks like toxicity and low therapeutic value. Therefore, there is a rising concern to develop new anti-leishmanial strategies. In this study, we report, for the first time, the one-pot synthesis method and functionalization of gold and silver nanoparticles with 4',7-dihydroxyflavone (Au-47DHF and Ag-47DHF) and their anti-leishmanial activity. Oval and spherical-shaped Au-47DHF nanoparticles were obtained with an average size of 5.8 ± 0.1 nm and while synthesized dodecahedron-shaped Ag-47DHF had an average size of 25.1 ± 1 nm. The zeta potential of Au-47DHF and Ag-47DHF were measured to be stable with values of 40 mV and 60 mV, respectively. The functionalization of nanoparticles with 4',7-dihydroxyflavone was confirmed by FTIR spectra. Both Au-

47DHF and Ag-47DHF exhibited promising anti-leishmanial activity against the promastigote forms with IC₅₀ values of 0.1226 ± 0.02 µg/ml and 0.8483 ± 0.14 µg/ml, respectively. The nanoparticles were also capable of anti-intracellular amastigote activity with 0.121 ± 0.36 µg/ml and 0.215 ± 0.85 µg/ml for Au-47DHF and Ag-47DHF, respectively. Interestingly, the treatment with Au-47DHF and Ag-47DHF nanoparticles generated high ROS concentrations in the parasites suggesting a ROS-mediated anti-leishmanial activity of Au-47DHF and Ag-47DHF. Concluding from the results, we present here a novel synthesis method of Au-47DHF and Ag-47DHF nanoparticles that have immense potential to be anti-leishmanial agents.

Gingival inflammation and hematological parameters in children with visceral leishmaniasis: A cross-sectional study.

Villibor, F., da Silva, L., Ribeiro, A., Guaré, R.

07-04-2022

Spec Care Dentist

<https://doi.org/10.1111/scd.12723>

This cross-sectional study aimed to assess gingival inflammation in 67 children aged 1-8 years (mean age 3.07) with visceral leishmaniasis (VL) at the time of hospitalization (D1) and 7 days after the first interview (D7) and compare the main hematological changes between the two time points. The biofilm index was verified at D1 and D7 using the Simplified Oral Hygiene Index (OHI-S) and the gingival inflammation index based on the gingival index (GI), along with hematological parameters. The mean OHI-S was 2.35 ± 0.93 at D1 and 1.47 ± 0.75 at D7. The mean GI was 0.56 ± 0.59 at D1 and 0.11 ± 0.32 at D7. The variable OHI-S at D1 could predict GI at D1, as an increase in the OHI-S value by one unit was associated with an increase in the GI D1 value by 0.36 units ($p < .05$). Multivariate linear regression analysis showed that none of the hematological variables were predictive of gingival inflammation at D1 and D7 ($p > .05$). Children with VL had poor oral hygiene on the first day of hospitalization. Clinically, the oral hygiene status progressed from poor at D1 to regular at D7. After 7 days the gingival bleeding scores also reduces.

Synthesis, in vitro antileishmanial efficacy and hit/lead identification of Nitrofurantoin-triazole hybrids.

Zuma, N., Aucamp, J., Viljoen, M., N'Da, D.

07-04-2022

ChemMedChem

<https://doi.org/10.1002/cmdc.202200023>

Leishmaniasis is a vector-borne neglected parasitic infection affecting thousands of individuals, mostly among populations in low- to moderate-income developing countries. In the absence of protective vaccines, the management of the disease banks solely on chemotherapy. However, the clinical usefulness of current antileishmanial drugs is threatened by their toxicity and the emergence of multidrug-resistant strains

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of the causative pathogens. This emphasizes the imperative for the development of new and effective antileishmanial agents. In this regard, we synthesized and evaluated in vitro the antileishmanial activity and cytotoxicity profile of a series of nitrofurantoin-triazole hybrids. The nitrofurantoin derivative 1 featuring propargyl moiety was distinctively the most active of all, was nontoxic to human cells and possessed submicromolar cellular activity selectively directed towards the pathogens of the life threatening visceral leishmaniasis. Hence it was identified as potential antileishmanial lead for further investigation into its prospective to act as alternative to therapies.

Immune response to LinB13, a *Lutzomyia intermedia* salivary protein correlates with disease severity in tegumentary leishmaniasis.

Carvalho, A., Viana, S., Andrade, B., Oliveira, F., Valenzuela, J., Carvalho, E., de Oliveira, C.

06-04-2022

Clin Infect Dis

<https://pubmed.ncbi.nlm.nih.gov/35385578>

We have previously shown that seropositivity to rLinB-13, a salivary protein from *Lutzomyia intermedia*, predicted sand fly exposure and was associated with increased risk of developing cutaneous leishmaniasis (CL). Herein, we investigated the cellular immune response to saliva from *Lu. intermedia*, using rLinB-13 as a surrogate antigen in naturally exposed individuals presenting positive serology to LinB-13. We also investigated the response to rLinB-13 in leishmaniasis patients, displaying active ulcers and positive PCR for *L. braziliensis*. Peripheral blood mononuclear cells (PBMCs) stimulated in vitro with rLinB-13 secreted elevated levels of IL-10, IL-4, IL-1 β , IL-1 α , IL-6 and chemokines (CCL3, CCL4, CCL5 and CXCL5). CL and disseminated leishmaniasis (DL) patients displayed a significantly higher IgG response to rLinB-13, compared to healthy subjects and anti-rLinB-13 IgG was positively correlated with the number of lesions in DL patients. Positive serology to rLinB-13 was also associated with chemotherapy failure. PBMCs from DL patients stimulated with rLINB-13 secreted significantly higher levels IL-10 and IL-1 β compared to CL individuals. In this study, we observed an association between humoral and cellular immune response to the sand fly salivary protein rLinB-13 and disease severity in tegumentary leishmaniasis. This study brings evidence that immunity to rLinB-13 influences disease outcome in *L. braziliensis* infection and results indicate that positive serology to rLinB-13 IgG can be employed as marker of DL, an emerging and severe form of disease caused by *L. braziliensis*.

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

Forrester, S., Gountry, A., Dias, B., Leal-Calvo, T., Moraes, M., Kaye, P., Mottram, J., Lima, A.

06-04-2022

Microbiol Spectr

<https://doi.org/10.1128/spectrum.00679-22>

Visceral leishmaniasis is associated with hepato-splenomegaly and altered immune and hematological parameters in both preclinical animal models and humans. We studied mouse experimental visceral leishmaniasis caused by *Leishmania infantum* and *Leishmania donovani* in BALB/c mice using dual RNA-seq to investigate the transcriptional response of host and parasite in liver and spleen. We identified only 4 species-specific parasite expressed genes (SSPEGs; log2FC >1, FDR <0.05) in the infected spleen, and none in the infected liver. For the host transcriptome, we found 789 differentially expressed genes (DEGs; log2FC >1, FDR <0.05) in the spleen that were common to both infections, with IFNy signaling and complement and coagulation cascade pathways highly enriched, and an additional 286 and 186 DEGs that were selective to *L. donovani* and *L. infantum* infection, respectively. Among those, there were network interactions between genes of amino acid metabolism and PPAR signaling in *L. donovani* infection and increased IL1 β and positive regulation of fatty acid transport in *L. infantum* infection, although no pathway enrichment was observed. In the liver, there were 1,939 DEGs in mice infected with either *L. infantum* or *L. donovani* in comparison to uninfected mice, and the most enriched pathways were IFNy signaling, neutrophil mediated immunity, complement and coagulation, cytokine-chemokine responses, and hemostasis. Additionally, 221 DEGs were selective in *L. donovani* and 429 DEGs in *L. infantum* infections. These data show that the host response for these two visceral leishmaniasis infection models is broadly similar, and ~10% of host DEGs vary in infections with either parasite species. **IMPORTANCE** Visceral leishmaniasis (VL) is caused by two species of *Leishmania* parasites, *L. donovani* in the Old World and *L. infantum* in the New World and countries bordering the Mediterranean. Although cardinal features such as hepato-splenomegaly and alterations in blood and immune function are evident, clinical presentation may vary by geography, with for example severe bleeding often associated with VL in Brazil. Although animal models of both *L. donovani* and *L. infantum* have been widely used to study disease pathogenesis, a direct side-by-side comparison of how these parasites species impact the infected host and/or how they might respond to the stresses of mammalian infection has not been previously reported. Identifying common and distinct pathways to pathogenesis will be important to ensure that new therapeutic or prophylactic approaches will be applicable across all forms of VL.

Blood Meal Analysis and Molecular Detection of *Leishmania* DNA in Wild-Caught Sand Flies in Leishmaniasis Endemic Areas of Turkey and Northern Cyprus.

Yetişmiş, K., Mert, U., Caner, A., Nalçacı, M., Töz, S., Özbel, Y.

06-04-2022

Acta Parasitol

<https://doi.org/10.1007/s11686-022-00542-4>

Phlebotomine sand flies (Diptera: Psychodidae) are known as

Leishmaniose

the vector of diseases such as leishmaniasis, bartonellosis and viral diseases. The aim of this study is to detect the host feeding pattern of sand flies in the endemic areas for leishmaniasis in Turkey (Antalya, Kayseri) and Northern Cyprus (TRNC) as well as the presence of Leishmania DNA in the specimens. One-hundred seventy-six blood-fed sand fly specimens were examined for blood meal analysis. A SYBR Green-PCR assay was performed with specific forward primers for each host and a universal reverse primer. Primers of human and goat were used together in multiplex PCR while goat and cow were studied separately. ITS-1 qPCR assay was also performed on both blood-fed and non-blood-fed females to detect Leishmania parasites. Blood sources could be detected in 69 out of 176 blood-fed sand fly specimens. The results of blood meal analysis showed that specimens were fed mostly on cows (22.2%) followed by humans (5.7%), goats (2.8%) and dogs (0.6%). Multiple feeding patterns were also detected as human+cow (3.4%), cow+goat (2.8%) and human+goat (1.7%). Five of the blood-fed specimens were Leishmania spp. positive: P. major s.l. (n=1), P. tobii (n=2) were L. tropica positive from Antalya, P. simici was positive for L. infantum from Kayseri and P. papatasi (n=1) was positive for L. major from Cyprus. Leishmania infection rates were determined as 3.79%, 1.69% and 2.63% among the blood-fed sand fly specimens in Antalya, Kayseri and TRNC, respectively. The SYBR-Green-based multiplex PCR assay is a cost-effective and promising tool for blood meal identification of wild-caught sand flies as well as other blood-sucking arthropods. Feeding patterns of important vector species detected in the present study show the high risk in these endemic areas. As a next step, to identify the blood source in a shorter time and to make the test more sensitive, development of this assay to probe-based and multiplex PCR will be also planned.

Identification of *Leishmania infantum* and *Leishmania braziliensis* in captive primates from a zoo in Brazil.

Guiraldi, L., Dos Santos, W., Manzini, S., Taha, N., Aires, I., Ribeiro, E., Tokuda, M., de Medeiros, M., Richini-Pereira, V., Lucheis, S.

05-04-2022

Am J Primatol

<https://doi.org/10.1002/ajp.23376>

Wild nonhuman primates (NHP) are considered natural hosts of a protozoan parasite from the genus Leishmania, the etiological agent of leishmaniasis. It is important to study the population of this infectious agent in zoo animals to establish surveillance and control mechanisms in Sorocaba through the application of a One Health approach, this is where human-animal-environment health and disease interface and can aid in the protection of endangered species. This study aimed to identify Leishmania infantum and Leishmania braziliensis in NHP living in a city where leishmaniasis is endemic. DNA was extracted from 48 NHP and analyzed using polymerase chain reaction primers that are specific for the species L. infantum and L. braziliensis. The results of our research revealed the first report of L. infantum and L. braziliensis naturally infecting

primates at Sorocaba zoo. One primate from the species Plecturocebus vieirai was positive for L. infantum and five primates (four Alouatta caraya and one Ateles chamek) were positive for L. braziliensis. This indicates a possible role of these animals on the maintenance of these parasites.

Aurothiomalate-Based Drugs as Potentially Novel Agents Against *Leishmania major*: A Mini Review.

Revue de littérature

Davoodi, A., Eslami, S., Fakhar, M., Aazadbakht, M., Montazeri, M., Khoshvishkaie, E., Keighobadi, M.

05-04-2022

Acta Parasitol

<https://doi.org/10.1007/s11686-022-00536-2>

Leishmaniasis is a major public health problem worldwide in many parts of the world. Current anti-leishmanial drugs have only limited clinical efficacy. Aurothiomalate derivatives are useful for treating rheumatoid arthritis, but have emerged as a promising therapeutic candidate for leishmaniasis. This paper gives a review of the literature about the usefulness of aurothiomalate derivatives against leishmaniasis. In this study, we reviewed the proposed mechanisms of action of aurothiomalate and related compounds on the metabolism of L. major and collected data by searching relevant articles. Aurothiomalate-based drugs could be effective against leishmaniasis through two direct and indirect mechanisms: first, cytotoxic effects on parasites via thiomalate's false substrate role in the citric acid cycle against malate; and second, immunosuppressive and anti-inflammatory effects of aurothiomalate derivatives with prostaglandin production inhibitory effects. The current study documented that aurothiomalate-based drugs could be effective against leishmaniasis through two direct and indirect mechanisms of action. Gold thiomalate as a promising hit should be evaluated against L. major in vitro and in vivo conditions in the future.

GIP: an open-source computational pipeline for mapping genomic instability from protists to cancer cells.

Späth, G., Bussotti, G.

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Nucleic Acids Res

<https://doi.org/10.1093/nar/gkab1237>

Genome instability has been recognized as a key driver for microbial and cancer adaptation and thus plays a central role in many diseases. Genome instability encompasses different types of genomic alterations, yet most available genome analysis software are limited to just one type of mutation. To overcome this limitation and better understand the role of genetic changes in enhancing pathogenicity we established GIP, a novel, powerful bioinformatic pipeline for comparative genome analysis. Here, we show its application to whole genome sequencing datasets of Leishmania, Plasmodium, Candida and cancer. Applying GIP on available data sets validated our pipeline and demonstrated the power of our

Cysticercose

tool to drive biological discovery. Applied to *Plasmodium vivax* genomes, our pipeline uncovered the convergent amplification of erythrocyte binding proteins and identified a nullisomic strain. Re-analyzing genomes of drug adapted *Candida albicans* strains revealed correlated copy number variations of functionally related genes, strongly supporting a mechanism of epistatic adaptation through interacting gene-dosage changes. Our results illustrate how GIP can be used for the identification of aneuploidy, gene copy number variations, changes in nucleic acid sequences, and chromosomal rearrangements. Altogether, GIP can shed light on the genetic bases of cell adaptation and drive disease biomarker discovery.

CYSTICERCOSE

Prevalence and factors associated with human *Taenia solium* taeniosis and cysticercosis in twelve remote villages of Ranomafana rainforest, Madagascar.

Rahantamalala, A., Rakotoarison, R., Rakotomalala, E., Rakotondrazaka, M., Kiernan, J., Castle, P., Hakami, L., Choi, K., Rafalimanantsoa, A., Harimanana, A., Wright, P., Grandjean Lapierre, S., Schoenhals, M., Small, P., Marcos, L., Vigan-Womas, I.

11-04-2022

PLoS Negl Trop Dis

<https://doi.org/10.1371/journal.pntd.0010265>

Infections with the tapeworm *Taenia solium* (taeniosis and cysticercosis) are Neglected Tropical Diseases (NTD) highly endemic in Madagascar. These infections are however underdiagnosed, underreported and their burden at the community level remains unknown especially in rural remote settings. This study aims at assessing the prevalence of *T. solium* infections and associated risk factors in twelve remote villages surrounding Ranomafana National Park (RNP), Ifanadiana District, Madagascar. A community based cross-sectional survey was conducted in June 2016. Stool and serum samples were collected from participants. Tapeworm carriers were identified by stool examination. Taenia species and *T. solium* genotypes were characterised by PCR and sequencing of the mitochondrial cytochrome c oxidase subunit 1 (cox1) gene. Detection of specific anti-cysticercal antibodies (IgG) or circulating cysticercal antigens was performed by ELISA or EITB/Western blot assays. Of the 459 participants with paired stool and blood samples included ten participants from seven distinct villages harbored *Taenia* spp. eggs in their stools samples DNA sequencing of the cox1 gene revealed a majority of *T. solium* Asian genotype (9/10) carriage. The overall seroprevalences of anti-cysticercal IgGs detected by ELISA and EITB were quite similar (27.5% and 29.8% respectively). A prevalence rate of 12.4% of circulating cysticercal antigens was observed reflecting cysticercosis with viable cysts. Open defecation (Odds Ratio, OR = 1.5, 95% CI: 1.0-2.3) and

promiscuity with households of more than 4 people (OR = 1.9, 95% CI: 1.1-3.1) seem to be the main risk factors associated with anticysticercal antibodies detection. Being over 15 years of age would be a risk factor associated with an active cysticercosis (OR = 1.6, 95% CI: 1.0-2.7). Females (OR = 0.5, 95% CI: 0.3-0.9) and use of river as house water source (OR = 0.3, 95% CI: 0.1-1.5) were less likely to have cysticercosis with viable cysts. This study indicates a high exposure of the investigated population to *T. solium* infections with a high prevalence of cysticercosis with viable cysts. These data can be useful to strengthen public health interventions in these remote settings.

CYSTICERCOSIS & HEART: A systematic review.

Revue de littérature

García-Martínez, C., Scatularo, C., Farina, J., Saldarriaga, C., Pérez, G., Wyss, F., Spina, S., Mendoza, I., Santi, R., Martínez-Sellés, M., Baranchuk, A.

05-04-2022

Curr Probl Cardiol

<https://pubmed.ncbi.nlm.nih.gov/35395330>

Cysticercosis is a parasitic tissue infection caused by larval cysts of the tapeworm *Taenia solium*. These larval cysts infect brain, muscle, or other tissue, and are a major cause of adult-onset seizures in most low-income countries with tropical climate. Prevalence it's around 50 million people. Although cardiovascular system is not the most affected, this disease can also be associated with multiple and randomly distributed cysts in the subpericardium, subendocardium and myocardium in up to 25% of infected patients. Most cardiac cysticercosis' cases are asymptomatic, but it can manifest with ventricular arrhythmias and conduction disorders. Area Covered: The "Neglected Tropical Diseases and other Infectious Diseases affecting the Heart" (NET-Heart project) is an initiative by the Emerging Leaders group of the Interamerican Society of Cardiology to systematically review all these endemic conditions affecting the heart. A systematic review was conducted following PRISMA guidelines and including articles published in MEDLINE, ScienceDirect, PubMed and LILACS databases. A total of 41 papers were included in this review. Expert Opinion: In the areas of greatest prevalence, unhealthiness and poverty favor the development of this disease, which highlights the need to establish global health policies that reduce morbidity and mortality, economic losses of the affected population, and health costs related to hospitalizations for cardiovascular involvement. Authors provide an algorithm to evaluate the possibility of Cysticercosis' cardiovascular complications.

DRACUNCULOSE

ECHINOCOCOSE

AN 8-YEAR-OLD CALIFORNIA GIRL WITH ASYMPOTOMATIC HEPATIC CYSTS.

Passarelli, P., Ramchandar, N., Naheedy, J., Kling, K., Choi, L., Pong, A.

11-04-2022

Pediatr Infect Dis J

<https://doi.org/10.1097/INF.0000000000003539>

Echinococcus infections are rare in the United States but may present a growing public health threat. We present the case of an 8-year-old female patient from Southern California who was diagnosed with hepatic echinococcosis after the incidental discovery of large hepatic cysts.

Hydatid cyst of the liver fistulized into the inferior vena cava.

Ben Ismail, I., Sghaier, M., Boujamil, K., Rebii, S., Zoghlaoui, A.

09-04-2022

Int J Surg Case Rep

<https://pubmed.ncbi.nlm.nih.gov/35413675>

Fistulization or rupture of hydatid liver cysts to the inferior vena cava (IVC) is an extremely rare and life-threatening condition. We report the case of a 70-year-old patient who presented with right-upper-quadrant pain and fullness evolving for 03 months. Physical examination showed dilated veins over the anterior abdominal wall and the flanks associated with lower-extremity swelling. Computed tomograph of the abdomen showed a hydatid cyst invading segments VI and VII of the liver fistulized into the inferior vena cava. The IVC was partially thrombosed. The diagnosis of a possibly ruptured hydatid cyst in the inferior vena cava was then made. The patient underwent surgical management. Per-operatively the cystic cavity had bloody content but the cysto-vascular communication was not identified. Partial cystectomy was performed leaving a fairly extensive contact between the calcified pericyst and the IVC. The postoperative course was uneventful. Rupture of the hepatic hydatid cyst into the IVC is very rare and may lead to fatal pulmonary embolism secondary to the migration of vesicles in the pulmonary artery or haemorrhagic shock. CT scan remains the best investigation method to assess the vascular links of the hepatic hydatid cyst especially with the IVC. Surgical treatment of the hepatic hydatid cyst ruptured into the IVC mandates vascular control before the hydatid cyst is punctured or removed. Fistulized hydatid cysts into the IVC should be operated on in centres equipped for extracorporeal bypass techniques, and experienced in the surgery of hepatic echinococcosis.

Efficient delivery of Echinococcus multilocularis miRNAs using chitosan nanoparticles.

Sun, Y., Kou, Y., He, X., Yan, Y., Guo, X., Yang, X., He, N., Cho, W., Kutyrev, I., Harandi, M., Kandil, O., Wang, X., Song, H., Zheng, Y.

08-04-2022

Biomed Pharmacother

<https://pubmed.ncbi.nlm.nih.gov/35405393>

Alveolar echinococcosis caused by *Echinococcus multilocularis* is an important zoonotic disease, a great threat to human health due to limited interventions. microRNAs are a type of small non-coding RNA that plays a key role in many diseases and is considered as a potential therapeutic target for control of parasitic diseases. However, naked miRNAs are difficult to enter into cells and are easily degraded in both external and internal environments. Chitosan (CS) has recently been used as a promising vehicle for delivery of nucleic acids. Therefore, we prepared miRNA-bearing CS nanoparticles and investigated the physicochemical properties as well as the delivery efficiency. We found that CS nanoparticles was relatively stable, offered miRNA strong protection from degradation and had low cytotoxicity with no significant effects on cell proliferation and apoptosis. CS nanoparticles were shown to be easily absorbed by cells and have remarkable liver tropism. Furthermore, CS nanoparticles were used to efficiently deliver *E. multilocularis* miR-4989 in vitro and in vivo and caused a significant reduction in the expression of UBE2N in the liver, a potential target of emu-miR-4989, at both mRNA and protein levels. Our data demonstrate that CS nanoparticles can act as a vehicle for efficient liver-targeted delivery of miRNAs and for development of miRNA-based therapeutics against *E. multilocularis* infection.

High variability in the number of *E. multilocularis* eggs in cat feces collected in the field.

Umhang, G., Bastien, M., Bastid, V., Poulle, M., Boué, F.

06-04-2022

Parasitol Int

<https://pubmed.ncbi.nlm.nih.gov/35398276>

Echinococcus multilocularis is the causative agent of alveolar echinococcosis that is considered as the most severe parasitic disease in Europe. The contribution of cat to environmental contamination by *E. multilocularis* is generally considered as extremely low based on results of experimental infections and worm burden estimations from natural infections. However, the recent collection of numerous cat feces from kitchen gardens in high endemic areas and the detection of *E. multilocularis* DNA in a significant number of these feces raise the question of the risk of human transmission from cats. This study aimed to provide a quantitative estimation of *E. multilocularis* eggs in feces from naturally infected cats. A field sampling conducted in 192 kitchen gardens during a joint study led to the collection and analysis of 597 cat feces, among them 7 (1.2%) yielded positive results for *E. multilocularis* real-time PCR. The entire pellets obtained after homogenization, filtration and centrifugation of a 5 g-sample for each of these 7 feces were examined under a stereoscopic microscope. After assessing their number, 20 taeniid eggs were individually isolated and specifically identified by real-time PCR. Morphologically mature *E. multilocularis* eggs were identified in 4 samples and the counting of 4 to 43 *E.*

multilocularis eggs per gram in these samples, i.e. 62 to 2331 eggs per feces when the total mass of the feces is considered. The number of eggs counted in 2 feces suggests a biotic potential of some naturally infected cats that largely exceed the previous experimental estimations.

A case of alveolar echinococcosis in the liver that ruptured into the pericardium treated by a combination of hepatectomy and albendazole.

Yamamoto, Y., Sakamoto, Y., Kamiyama, T., Nagatsu, A., Asahi, Y., Orimo, T., Kakisaka, T., Kamachi, H., Otsuka, T., Mitsuhashi, T., Taketomi, A.

08-04-2022

Surg Case Rep

<https://doi.org/10.1186/s40792-022-01417-6>

Alveolar echinococcosis (AE) is a rare parasitic disease caused by the larva of *Echinococcus multilocularis*. It nearly always occurs in the liver, and cardiac involvement is extremely rare. Liver resection is the most effective intervention for AE because the only potentially curative treatment is removal of the lesion. Even when complete resection is not performed, long-term survival can be expected after surgical removal of most of the lesion with lifelong administration of albendazole (ABZ). A 64-year-old man who lived in Hokkaido was referred to our hospital due to abnormalities in biliary enzymes. According to the findings from enhanced computed tomography and magnetic resonance imaging of the abdomen, transthoracic echocardiography and serologic tests, he was diagnosed with hepatic AE with rupture into the pericardium. He underwent extended left hemi-hepatectomy with reconstruction of the inferior vena cava and opening of the pericardium with drainage as reduction surgery. Pathological examination revealed echinococcal infection in the pericardium as well as the liver. He started chemotherapy with 400 mg ABZ per Day 67 days after surgery. Although the surgical margin was positive in the pathological findings, he was alive 19 months later with no regrowth of the echinococcal lesion. AE with cardiac involvement is extremely rare. Even if the complete removal of cardiac-involved AE is not possible, surgical debulking with lifelong ABZ treatment can successfully manage the disease.

TREMATODESES D'ORIGINE ALIMENTAIRE (CLONORCHIASIS, OPISTHORCHIASIS, FASCIOLASE ET PARAGONIMOSE)

FILARIOSE LYMPHATIQUE

Community-based trial assessing the impact of annual versus semiannual mass drug administration with ivermectin plus albendazole and praziquantel on helminth infections in northwestern Liberia.

Eneanya, O., Gankpala, L., Goss, C., Momolu, A., Nyan, E., Gray, E., Fischer, K., Curtis, K., Bolay, F., Weil, G., Fischer, P.

08-04-2022

Acta Trop

<https://pubmed.ncbi.nlm.nih.gov/35405102>

We assessed the impact of three annual vs five semiannual rounds of mass drug administration (MDA) with ivermectin plus albendazole followed by praziquantel for the control or elimination of lymphatic filariasis (LF), onchocerciasis, soil-transmitted helminth (STH) infections and schistosomiasis in Lofa County, Liberia. The study started in 2012 and was interrupted in 2014 during the Ebola virus outbreak. Repeated cross-sectional surveys were conducted in individuals 5 years and older to measure infection markers. Wuchereria bancrofti antigenemia prevalences decreased from 12.5 to 1.2% (90% reduction) and from 13.6 to 4.2% (69% reduction) one year after three rounds of annual or five rounds of semiannual MDA, respectively. Mixed effects logistic regression models showed decreases in odds of antigenemia positivity were 91 and 74% at that time in the annual and semiannual treatment zones, respectively ($p < 0.001$). Semiannual MDA was slightly more effective for reducing *Onchocerca volvulus* microfiladermia prevalence and at follow-up 3 were 74% (from 14.4 to 3.7%) and 83% (from 23.6 to 4.5%) in the annual and semiannual treatment zones, respectively. Both treatment schedules had similar beneficial effects on hookworm prevalence. Thus, annual and semiannual MDA with ivermectin and albendazole had similar beneficial impacts on LF, onchocerciasis, and STH in this setting. In contrast, MDA with praziquantel had little impact on hyperendemic *Schistosoma mansoni* in the study area. Results from a long-term follow-up survey showed that improvements in infection parameters were sustained by routine annual MDA provided by the Liberian Ministry of Health after our study endpoint.

Spatial transcriptomics reveals antiparasitic targets associated with essential behaviors in the human parasite *Brugia malayi*.

Airs, P., Vaccaro, K., Gallo, K., Dingirard, N., Heimark, Z., Wheeler, N., He, J., Weiss, K., Schroeder, N., Huisken, J., Zamanian, M.

07-04-2022

PLoS Pathog

<https://doi.org/10.1371/journal.ppat.1010399>

Lymphatic filariasis (LF) is a chronic debilitating neglected tropical disease (NTD) caused by mosquito-transmitted nematodes that afflicts over 60 million people. Control of LF relies on routine mass drug administration with antiparasitics

that clear circulating larval parasites but are ineffective against adults. The development of effective adulticides is hampered by a poor understanding of the processes and tissues driving parasite survival in the host. The adult filariae head region contains essential tissues that control parasite feeding, sensory, secretory, and reproductive behaviors, which express promising molecular substrates for the development of antifilarial drugs, vaccines, and diagnostics. We have adapted spatial transcriptomic approaches to map gene expression patterns across these prioritized but historically intractable head tissues. Spatial and tissue-resolved data reveal distinct biases in the origins of known drug targets and secreted antigens. These data were used to identify potential new drug and vaccine targets, including putative hidden antigens expressed in the alimentary canal, and to spatially associate receptor subunits belonging to druggable families. Spatial transcriptomic approaches provide a powerful resource to aid gene function inference and seed antiparasitic discovery pipelines across helminths of relevance to human and animal health.

MYCETOME

Eumycetoma Causative Agents are Inhibited in vitro by Luliconazole, Lanoconazole and Ravaconazole.

Nyuykonge, B., Lim, W., van Amelsvoort, L., Bonifaz, A., Fahal, A., Badali, H., Abbastabar, M., Verbon, A., van de Sande, W.
 10-04-2022
Mycoses
<https://doi.org/10.1111/myc.13442>

Eumycetoma is a subcutaneous mutilating disease that can be caused by many different fungi. Current treatment consists of prolonged itraconazole administration in combination with surgery. In many centers, due to their slow growth rate, the treatment for eumycetoma is often started before the causative agent is identified. This harbors the risk that the causative fungus is not susceptible to the given empirical therapy. In the open-source drug program MycetOS, ravaconazole and luliconazole were promising antifungal agents that were able to inhibit the growth of *Madurella mycetomatis*, the most common causative agent of mycetoma. However, it is currently not known whether these drugs inhibit the growth of other eumycetoma causative agents. Here, we determined the in vitro activity of luliconazole, lanoconazole and ravaconazole against commonly encountered eumycetoma causative agents. MICs were determined for lanoconazole, luliconazole and ravaconazole against 37 fungal isolates which included *Madurella* species, *Falciformispora senegalensis*, *Medicopsis romeroi* and *Trematosphaeria grisea* and compared to those of itraconazole. Ravaconazole, luliconazole and lanoconazole showed high activity against all eumycetoma causative agents tested with median MICs ranging from 0.008-2 µg/ml, 0.001-

0.064 µg/ml and 0.001-0.064 µg/ml, respectively. Even *Ma. fahalii* and *Me. romeroi*, which are not inhibited in growth by itraconazole at a concentration of 4 µg/ml, were inhibited by these azoles. The commonly encountered eumycetoma causative agents are inhibited by lanoconazole, luliconazole and ravaconazole. These drugs are promising candidates for further evaluation as potential treatment for eumycetoma.

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

Irinyi, L., Roper, M., Meyer, W.

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Med Mycol

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

Scedosporium species are emerging opportunistic fungal pathogens causing various infections mainly in immunocompromised patients, but also in immunocompetent individuals, following traumatic injuries. Clinical manifestations range from local infections, such as subcutaneous mycetoma or bone and joint infections, to pulmonary colonization and severe disseminated diseases. They are commonly found in soil and other environmental sources. To date *S. aurantiacum* has been reported only from a handful of countries. To identify the worldwide distribution of this species we screened publicly available sequencing data from fungal metabarcoding studies in the Sequence Read Archive (SRA) of The National Centre for Biotechnology Information (NCBI) by multiple BLAST searches. *S. aurantiacum* was found in 26 countries and two islands, throughout every climatic region. This distribution is like that of other *Scedosporium* species. Several new environmental sources of *S. aurantiacum* including human and bovine milk, chicken and canine gut, freshwater, and feces of the giant white-tailed rat (*Uromys caudimaculatus*) were identified. This study demonstrated that raw sequence data stored in the SRA database can be repurposed using a big data analysis approach to answer biological questions of interest. To understand the distribution and natural habitat of *S. aurantiacum*, species-specific DNA sequences were searched in the SRA database. Our large-scale data analysis illustrates that *S. aurantiacum* is more widely distributed than previously thought and new environmental sources were identified.

ONCHOCERCOSE

Extensive aberrant migration of *Onchocerca lupi* in a dog.

Wallitsch, K., Jaffey, J., Ferguson, S., Verocai, G., Sobotyk, C., van Eerde, E., Bashaw, S.

10-04-2022

Top Companion Anim Med

<https://pubmed.ncbi.nlm.nih.gov/35417784>

A 13-year-old Labrador retriever mixed breed dog from Arizona was presented for evaluation of an acute onset of a head tilt as well as vocalization and head shaking upon palpation of the ears. The dog was previously treated for ocular onchocercosis associated with the right eye 10 years earlier. Ophthalmic examination at presentation revealed irregular, tan-colored, masses on the sclera of both eyes. Otoscopic evaluation of the left ear was limited because the canals were stenotic and inaccessible. Cytology did not reveal any infectious etiologies and the dog was subsequently treated with an anti-inflammatory dose of prednisone for 10 days. Two weeks later the dog developed a mild dysphonia and stridor that eventually progressed to include difficulty breathing. The dog was euthanized and post-mortem examination revealed white-to-tan nodules identified in the episclera, trachea, subcutis around the nares, external ear canals, and within the fascia overlying the temporalis muscle, as well as in the parietal pleura, and pericardium. There was also a large mass that obliterated the laryngeal cartilage that partially occluded the laryngeal opening. Microscopically, the described nodules consisted predominately of lakes of abundant mineralized debris, admixed with granulomatous inflammation centered around degenerate nematodes that were subsequently confirmed by PCR and sequence analysis to be *Onchocerca lupi*. The veterinary literature is comprised of only two reports that describe aberrant *O. lupi* migration to the trachea and larynx. Here, we provide the first detailed description of a dog with extensive aberrant onchocercosis.

Community-based trial assessing the impact of annual versus semiannual mass drug administration with ivermectin plus albendazole and praziquantel on helminth infections in northwestern Liberia.

Eneanya, O., Gankpala, L., Goss, C., Momolu, A., Nyan, E., Gray, E., Fischer, K., Curtis, K., Bolay, F., Weil, G., Fischer, P.

08-04-2022

Acta Trop

<https://pubmed.ncbi.nlm.nih.gov/35405102>

We assessed the impact of three annual vs five semiannual rounds of mass drug administration (MDA) with ivermectin plus albendazole followed by praziquantel for the control or elimination of lymphatic filariasis (LF), onchocerciasis, soil-transmitted helminth (STH) infections and schistosomiasis in Lofa County, Liberia. The study started in 2012 and was interrupted in 2014 during the Ebola virus outbreak. Repeated cross-sectional surveys were conducted in individuals 5 years and older to measure infection markers. Wuchereria bancrofti antigenemia prevalences decreased from 12.5 to 1.2% (90% reduction) and from 13.6 to 4.2% (69% reduction) one year after three rounds of annual or five rounds of semiannual MDA, respectively. Mixed effects logistic regression models showed decreases in odds of antigenemia positivity were 91 and 74% at that time in the annual and semiannual treatment zones, respectively ($p < 0.001$). Semiannual MDA was slightly more effective for reducing *Onchocerca volvulus* microfiladermia prevalence and at follow-up 3 were 74% (from 14.4 to 3.7%) and 83% (from 23.6 to 4.5%) in the annual and semiannual treatment zones, respectively. Both treatment schedules had similar beneficial effects on hookworm prevalence. Thus, annual and semiannual MDA with ivermectin and albendazole had similar beneficial impacts on LF, onchocerciasis, and STH in this setting. In contrast, MDA with praziquantel had little impact on hyperendemic *Schistosoma mansoni* in the study area. Results from a long-

zones, respectively ($p < 0.001$). Semiannual MDA was slightly more effective for reducing *Onchocerca volvulus* microfiladermia prevalence and at follow-up 3 were 74% (from 14.4 to 3.7%) and 83% (from 23.6 to 4.5%) in the annual and semiannual treatment zones, respectively. Both treatment schedules had similar beneficial effects on hookworm prevalence. Thus, annual and semiannual MDA with ivermectin and albendazole had similar beneficial impacts on LF, onchocerciasis, and STH in this setting. In contrast, MDA with praziquantel had little impact on hyperendemic *Schistosoma mansoni* in the study area. Results from a long-term follow-up survey showed that improvements in infection parameters were sustained by routine annual MDA provided by the Liberian Ministry of Health after our study endpoint.

SCHISTOSOMIASIS

Community-based trial assessing the impact of annual versus semiannual mass drug administration with ivermectin plus albendazole and praziquantel on helminth infections in northwestern Liberia.

Eneanya, O., Gankpala, L., Goss, C., Momolu, A., Nyan, E., Gray, E., Fischer, K., Curtis, K., Bolay, F., Weil, G., Fischer, P.

08-04-2022

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We assessed the impact of three annual vs five semiannual rounds of mass drug administration (MDA) with ivermectin plus albendazole followed by praziquantel for the control or elimination of lymphatic filariasis (LF), onchocerciasis, soil-transmitted helminth (STH) infections and schistosomiasis in Lofa County, Liberia. The study started in 2012 and was interrupted in 2014 during the Ebola virus outbreak. Repeated cross-sectional surveys were conducted in individuals 5 years and older to measure infection markers. Wuchereria bancrofti antigenemia prevalences decreased from 12.5 to 1.2% (90% reduction) and from 13.6 to 4.2% (69% reduction) one year after three rounds of annual or five rounds of semiannual MDA, respectively. Mixed effects logistic regression models showed decreases in odds of antigenemia positivity were 91 and 74% at that time in the annual and semiannual treatment zones, respectively ($p < 0.001$). Semiannual MDA was slightly more effective for reducing *Onchocerca volvulus* microfiladermia prevalence and at follow-up 3 were 74% (from 14.4 to 3.7%) and 83% (from 23.6 to 4.5%) in the annual and semiannual treatment zones, respectively. Both treatment schedules had similar beneficial effects on hookworm prevalence. Thus, annual and semiannual MDA with ivermectin and albendazole had similar beneficial impacts on LF, onchocerciasis, and STH in this setting. In contrast, MDA with praziquantel had little impact on hyperendemic *Schistosoma mansoni* in the study area. Results from a long-

Schistosomiasis

term follow-up survey showed that improvements in infection parameters were sustained by routine annual MDA provided by the Liberian Ministry of Health after our study endpoint.

Approaches to advance drug discovery for neglected tropical diseases.

Revue de littérature

Ferreira, L., de Moraes, J., Andricopulo, A.

07-04-2022

Drug Discov Today

<https://pubmed.ncbi.nlm.nih.gov/35398562>

Neglected tropical diseases (NTDs), which include leishmaniasis, Chagas disease, human African trypanosomiasis (HAT), and schistosomiasis, remain public health problems in developing countries, as highlighted in the 2021-2030 WHO Roadmap on NTDs. This agenda sets the challenges for the control and elimination of NTDs by 2030. Fortunately, NTD drug discovery has shifted from traditional to modern strategies combining medicinal chemistry, phenotypic and molecular assays, multiparameter optimization, structural biology, and 'omics approaches. Structure- and ligand-based drug design have fostered NTD drug discovery by enabling data-driven molecular optimization, expansion to previously inaccessible chemical spaces, and knowledge building from biological data. These efforts have integrated parasite biology and medicinal chemistry to advance drug discovery in this key area of global health. Teaser: Novel knowledge on parasite biology and medicinal chemistry has been key to advancing structure- and ligand-based NTD drug discovery.

In vitro and in vivo impacts of nifedipine and diltiazem on praziquantel chemotherapy in murine Schistosoma mansoni.

Adel Madbouly, N., Emam, M., Ayman, M., Ayman, M., Rabia, I., El Amir, A.

06-04-2022

Exp Parasitol

<https://pubmed.ncbi.nlm.nih.gov/35398100>

This study was planned to evaluate the in vitro and in vivo antischistosomal effects of the widely used antihypertensive drugs, nifedipine (NIF) and diltiazem (DTZ), and their combinations with praziquantel (PZQ) on early and late *Schistosoma (S.) mansoni* infections 21- and 45- days old stages. In the In vitro study, Calcium channel blockers (CCBs), NIF and DTZ were added to schistosomula and adult worm cultures in different concentrations 10, 20 and 30 mg/ml. The mortality percentage was calculated 1, 12 and 24 h after incubation. In vivo, NIF and DTZ either alone or combined with PZQ were used to treat male albino mice. The parasitological and total immunoglobulin (Ig) G and IgM anti-soluble egg antigen (SEA) were assessed to demonstrate the disease severity. In the In vitro study, 10 mg/ml NIF induced 100% mortality percentage of both schistosomula and adult worms after 24 h incubation, while DTZ induced similar mortality percentage at 30 mg/ml concentration. In vivo results showed

that early or late combination of 30 mg/kg of NIF, but not DTZ, significantly ($P < 0.05$) enhanced the reductive efficacy of PZQ based on the parasitological data. The maximal reduction ($P < 0.05$) of anti-SEA IgM and IgG levels was developed during NIF-PZQ administration 21- (1.12 ± 0.06 and 1.09 ± 0.04 , respectively) or 45- (1.00 ± 0.03 and 0.8 ± 0.06 , respectively) days post infection (PI), compared to either PZQ or NIF individual treatments. The decreased concentration of anti-SEA antibodies was correlated with the diminished granulomatous diameter and disease severity. Nifedipine improved PZQ chemotherapy targeting either early or late *S. mansoni* infection in mice compared to the PZQ mono-therapy. Administering NIF can be considered as a promising drug candidate for schistosomiasis chemotherapy.

Blocking prostanoid receptors switches on multiple immune responses and cascades of inflammatory signaling against larval stages in snail fever.

Revue de littérature

Saber, S., Alomar, S., Yahya, G.

09-04-2022

Environ Sci Pollut Res Int

<https://doi.org/10.1007/s11356-022-20108-1>

Schistosomiasis, also known as snail fever or bilharziasis, is a worm infection caused by trematode called schistosomes that affects humans and animals worldwide. Schistosomiasis endemically exists in developing countries. Inflammatory responses elicited in the early phase of infection represent the rate limiting step for parasite migration and pathogenesis and could be a valuable target for therapeutic interventions. Prostaglandin E2 (PGE2) and interleukin (IL)-10 were found to be differentially affected in case of immune-modulation studies and cytokine analysis of hosts infected with either normal or radiation-attenuated parasite (RA) which switches off the development of an effective immune response against the migrating parasite in the early phase of schistosomiasis. Normal parasites induce predominantly a T helper 2 (Th2)-type cytokine response (IL-4 and IL-5) which is essential for parasite survival; here, we discuss in detail the downstream effects and cascades of inflammatory signaling of PGE2 and IL10 induced by normal parasites and the effect of blocking PGE2 receptors. We suggest that by selectively constraining the production of PGE2 during vaccination or therapy of susceptible persons or infected patients of schistosomiasis, this would boost IL-12 and reduce IL-10 production leading to a polarization toward the anti-worm Th1 cytokine synthesis (IL-2 and Interferon (IFN)- γ).

Co-infections of *Schistosoma spp.* and malaria with hepatitis viruses from endemic countries: A systematic review and meta-analysis.

Taghipour, A., Bahadory, S., Olfatifar, M., Norouzi, M., Majidiani, H., Foroutan, M.

06-04-2022

Infect Disord Drug Targets

<https://doi.org/10.2174/187152652266220406122742>

Co-infection of schistosomiasis and malaria with hepatitis B virus (HBV) and hepatitis C virus (HCV) are common in countries where schistosomiasis and malaria are endemic. The present systematic review and meta-analysis was conducted to assess the prevalence of malaria/hepatitis viruses and Schistosoma/hepatitis viruses' co-infections. Relevant published studies on the co-infection of malaria and Schistosoma spp. with HBV and HCV were retrieved via international databases (PubMed, Scopus, Web of Science, and Google Scholar). Regarding meta-analysis, the random-effect model was employed by forest plot with 95% of confidence interval (CI). A total of 22 studies, including 15 studies with malaria/hepatitis viruses' co-infection and 7 studies with Schistosoma/hepatitis viruses' co-infection met the eligibility criteria. The co-infection of malaria/HCV and malaria/HBV in different populations were 15% (95% CI, 0-77%) and 5% (95% CI, 1-10%), respectively. Moreover, Schistosoma/HCV and Schistosoma/HBV co-infection were detected in 7% (95% CI, 0-54%) and 2% (95% CI, 0-7%), respectively. The overlaps between Schistosoma spp. and malaria with hepatitis B and C viruses in endemic countries with lower income levels were high, which deserve further attention.

A chromosome-level genome of the human blood fluke *Schistosoma japonicum* identifies the genomic basis of host-switching.

Luo, F., Yang, W., Yin, M., Mo, X., Pang, Y., Sun, C., Zhu, B., Zhang, W., Yi, C., Li, Z., Wang, J., Xu, B., Feng, Z., Huang, Y., Lu, Y., Hu, W.

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Cell Rep

<https://pubmed.ncbi.nlm.nih.gov/35385741>

The evolution and adaptation of *S. japonicum*, a zoonotic parasite that causes human schistosomiasis, remain unclear because of the lack of whole-genome data. We construct a chromosome-level *S. japonicum* genome and analyze it together with 72 samples representing six populations of the entire endemic region. We observe a Taiwan zoophilic lineage splitting from zoonotic populations ~45,000 years ago, consistent with the divergent history of their intermediate hosts. Interestingly, we detect a severe population bottleneck in *S. japonicum*, largely coinciding with human history in Asia during the last glacial maximum. We identify several genomic regions underlying natural selection, including GATAD2A and Lmln, both showing remarkable differentiation among different areas. RNAi knockdown suggests association of GATAD2A with parasite development and infection in definitive hosts, while Lmln relates to the specificity of the intermediate hosts. Our study provides insights into the evolution of *S. japonicum* and serves as a resource for further studies.

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

Prevalence and associated risk factors of soil-transmitted helminth infections in Kandahar, Afghanistan.

Rahimi, B., Mahboobi, B., Wafa, M., Sahrai, M., Stanikzai, M., Taylor, W.

11-04-2022

BMC Infect Dis

<https://doi.org/10.1186/s12879-022-07336-z>

Soil-transmitted helminth (STH) infections are still a major health problem, especially in resource-limited countries. The community-based prevalence of STH is unknown in Afghanistan. Main objectives of this study were to estimate the prevalence and associated factors of STH among children in Daman district of Kandahar province in Afghanistan. This was a community-based cross-sectional study, with data collected during five months (June-October, 2020) from children living in five villages of Daman district in Kandahar, Afghanistan. All the stool samples were examined by saline wet mount method. Data were analyzed by using descriptive statistics, Chi square test, and multivariate logistic regression. A total of 1426 children were studied, with majority (61.8%) of males and the mean age of 6.3 years. The overall prevalence of any intestinal parasitic infection was 39.8%. The overall prevalence of STH infection was 22.7%, with *Ascaris lumbricoides* (18.7%) as the most prevalent STH species, followed by hookworm (7.5%) and *Trichuris trichiura* (1.4%). Single, double, and triple STH infections were present in 14.9%, 7.2%, and 0.6% of the children, respectively. Multivariate logistic regression revealed that not washing hands after defecating/before eating (AOR 7.0, 95% CI 3.4-14.0), living in mud house (AOR 3.5, 95% CI 1.6-7.4), walking barefoot (AOR 2.2, 95% CI 1.6-3.1), living in overcrowded house (AOR 1.6, 95% CI 1.1-2.3), and practicing open defecation (AOR 1.4, 95% CI 1.1-2.0) as the risk factors associated with the predisposition of rural children for getting STH in Daman district of Afghanistan. Prevalence of STH is high among children of Daman district in Afghanistan. Most of the risk factors are related to poverty, decreased sanitation, and improper hygiene. Improvement of socioeconomic status, sanitation, and health education to promote public awareness about health and hygiene together with periodic mass deworming programs are better strategies for the control of STH infections in Afghanistan. Also, government and international donor agencies in Afghanistan should help in improving socio-economic status of the rural areas through provision of basic facilities such as piped water, electricity, good housing, and proper toilets.

Prevalence, intensity of infection and associated risk factors of soil-transmitted helminth infections among school children at Tachgayint woreda, Northcentral Ethiopia.

Eyayu, T., Yimer, G., Workineh, L., Tiruneh, T., Sema, M., Legese, B., Almaw, A., Solomon, Y., Malkamu, B., Chanie, E., Feleke, D., Jimma, M., Hassen, S., Tesfaw, A.

08-04-2022

PLOS One

<https://doi.org/10.1371/journal.pone.0266333>

Soil-transmitted helminths (STH) are one of the most common infections affecting underprivileged populations in low- and middle-income countries. Ascaris lumbricoides, Trichuris trichiura, and hookworm are the three main species that infect people. School children are the most vulnerable groups for STH infections due to their practice of walking and playing barefoot, poor personal hygiene, and environmental sanitation. However, evidence is limited in the study area. So, this study aimed to assess the current prevalence, infection intensity, and associated risk factors of STHs among school children in Tachgayint woreda, Northcentral Ethiopia. A cross-sectional study was conducted among school children of Tachgayint woreda from February to May 2021. The study participants were chosen via systematic random sampling. Stool samples were collected from 325 children and examined using the Kato-Katz technique. The data was analyzed using SPSS version 23. Binary and multivariable logistic regression analyses were used to identify the potential associated factors for STHs. An adjusted odds ratio (AOR) with a 95% confidence interval (CI) was used to measure the magnitude of the association. A P-value <0.05 was considered statistically significant. The overall prevalence of STHs in this study was 36.0% (95% CI: 30.5-41.2%). Ascaris lumbricoides are the most prevalent species 89 (27.4%) followed by hookworm 14 (4.3%) and Trichuris trichiura 10 (3.1%). All of the infected school children had light-intensity of infections with the mean of eggs per gram (EPG) being 464.53. Lack of shoe wearing habit (AOR = 4.08, 95% CI: 1.29-12.88) and having untrimmed fingernail (AOR = 1.85, 95% CI: 1.06-3.22) were identified as risk factors for STH infections. More than one-third of the school children were infected with at least one STH species and this indicates that STHs are still a health problem among school children in the study area. Therefore, periodic deworming, implementation of different prevention strategies, and health education programs should be regularly applied in the area.

High intestinal parasite infection detected in children from Región Autónoma Atlántico Norte (R.A.N.) of Nicaragua.

Muñoz-Antoli, C., Pérez, P., Pavón, A., Toledo, R., Esteban, J.

07-04-2022

Sci Rep

<https://doi.org/10.1038/s41598-022-09756-y>

There is a lack of epidemiological information concerning intestinal parasitic infections, and especially in soil-transmitted helminths, occurring in some departments of Nicaragua. Up to

now, this is the first study involving two nearby areas (Puerto Cabezas and Siuna municipalities) of the Región Autónoma Atlántico Norte (R.A.A.N.). One stool sample was analyzed by Kato-Katz, formaldehyde-ethyl acetate concentration method and modified Ziehl-Neelsen technique, and a simple questionnaire concerning demographic, sanitary and behavioral data was distributed among 735 children and evaluated. Overall prevalence of infection reached 97.0%, being the highest prevalences detected in all Nicaragua. The higher protozoan prevalence appears in Siuna (94.5%), a rural interior municipality, with a typical tropical monsoon climate, while the higher helminths rates were reached in Puerto Cabezas (92.8%), the urbanized coastal capital, with a typical tropical rainforest climate. No statistical differences were found with regard to sex. However, the 6-11-year age-group children presented the highest prevalences. Most *T. trichiura* infections (59.4%) were of light intensity, while 51.7% of *Ascaris lumbricoides* were of moderate intensity. Multivariable logistic regression analysis indicated that those who drink rainwater and walk barefoot were 2.9 and 2.5 times more likely to have helminth infections, respectively. Results from one geographical setting might not be applied to other nearby with different climatic conditions. The use of anthelmintic drugs only will not be sufficient to bring prevalence to low levels. It is necessary to design geographically more specific intervention, with communication and interaction between different disciplines (e.g. parasitology, biochemistry, molecular biology, epidemiology, public health, etc.) being imperative to reduce STH infection.

Molecular epidemiology of Ascaris species recovered from humans and pigs in Cameroon.

Nkouayep, V., McManus, D., Mbida, M., Gordon, C., Nejsum, P.

06-04-2022

Trans R Soc Trop Med Hyg

<https://pubmed.ncbi.nlm.nih.gov/35385862>

In Cameroon, considerable research has been conducted on human ascariasis, but no studies have been undertaken to determine whether pigs contribute to the persistence of the infection in children or to unravel the evolutionary relationship between human-derived and pig-derived Ascaris. DNA was extracted from adult Ascaris worms collected from humans and pigs. Segments of the cytochrome c oxidase subunit 1 (cox1) and NADH dehydrogenase subunit 1 (nad1) genes were sequenced and analysed for 83 worms to dissect the local transmission dynamics of Ascaris in Cameroon. The data showed high genetic diversity and revealed demographically expanding populations in the human and pig Ascaris samples. A restricted gene flow between Ascaris lumbricoides and Ascaris suum populations correlating with the preference for humans and pigs, respectively, as hosts was evident. Phylogenetic analyses and haplotype networks split the haplotypes into two major clusters, A and B. However, support for cross-transmission between hosts and hybridization were revealed through shared haplotypes among worms from both hosts. This study provides useful baseline information for future studies of the genetics of

Ascaris in Cameroon and suggests that effective and sustainable control of human ascariasis should target both human and pig hosts.

GALE

Microscopic (video) demonstration of *Sarcoptes scabiei* mite.

**Sadhasivamohan, A., Palaniappan, V., Karthikeyan, K.,
Selvaarasan, J.**

07-04-2022

BMJ Case Rep

<https://pubmed.ncbi.nlm.nih.gov/35393284>

Use of oral ivermectin in permethrin-resistant scabies: A pilot study.

**Balestri, R., Magnano, M., Infusino, S., Rizzoli, L., Girardelli, C.,
Rech, G.**

06-04-2022

Dermatol Ther

<https://doi.org/10.1111/dth.15495>

MORSURES DE SERPENT