Réseau MTN Francophone

Veille scientifique
Maladies tropicales négligées

Semaine 23

06 juin 2022 – 13 juin 2022

DENGUE, CHIKUNGUNYA ET MALADIE A VIRUS ZIKA

Broad-spectrum anti-flavivirus activity and chemistry of compounds containing sulfur and oxygen chalcogens.

Revue de littérature

Sole Burali, M., Cecchetti, V., Manfroni, G.
10-06-2022
Curr Med Chem
https://doi.org/10.2174/0929867329666220610211441

Sulfur and oxygen containing-compounds are a relevant class of derivatives that is constantly growing due to their wide range of pharmacological activity, including the antiviral one. As a proof of this, there are several FDA approved antiviral compounds having sulfur and oxygen in their structures. Among RNA viruses, the flavivirus genus (e.g. Dengue, West Nile, Yellow Fever and Zika viruses) holds a relevant place within zoonotic pathogens and thus flavivirus infections are considered a growing risk for the public health. As a consequence, the drug discovery process aimed at identify new anti-flavivirus agents is of great relevance and will help to find effective therapies not available yet. One of the most alarming features of flaviviruses is their ability to co-infect the host, thus aggravating the symptoms of the disease. Therefore, finding compounds endowed with a broad-spectrum anti-flavivirus activity is now becoming a pressing need. In this review, we describe the most promising compounds having both sulfur and oxygen in their structures characterized by a broad-spectrum activity against different flaviviruses. Furthermore, the synthetic procedures applied for the preparation of the described derivatives are also reported. Readers can be inspired by the contents of this review to design and synthesize more effective anti-flavivirus agents as well as to select viral or host targets to achieve an antiviral activity as broad as possible.

Forecasting the incidence of dengue in Bangladesh-Application of time series model.

Naher, S., Rabbi, F., Hossain, M., Banik, R., Pervez, S., Boitchi, A.
08-06-2022
Health Sci Rep
https://doi.org/10.1002/hsr2.666

Background: Dengue is an alarming public health concern in terms of its preventive and curative measures among people in Bangladesh; moreover, its sudden outbreak created a lot of suffering among people in 2018. Considering the greater burden of disease in larger epidemic years and the difficulty in understanding current and future needs, it is highly needed to address early warning systems to control epidemics from the earliest. Objective: The study objective was to select the most appropriate model for dengue incidence and using the selected model, the authors forecast the future dengue outbreak in Bangladesh. Methods and Materials: This study considered a secondary data set of monthly dengue occurrences over the period of January 2008 to January 2020. Initially, the authors found the suitable model from Autoregressive Integrated Moving Average (ARIMA), Error, Trend, Seasonal (ETS) and Trigonometric seasonality, Box-Cox transformation, ARMA errors, Trend and Seasonal (TBATS) models with the help of selected model selection criteria and finally employing the selected model make forecasting of dengue incidences in Bangladesh. Results: Among ARIMA, ETS, and TBATS models, the ARIMA model performs better than others. The Box-Jenkin's procedure is applicable here and it is found that the best-selected model to forecast the dengue outbreak in the context of Bangladesh is ARIMA (2,1,2). Conclusion: Before establishing a comprehensive plan for future combating strategies, it is vital to understand the future scenario of dengue occurrence. With this in mind, the authors aimed to select an appropriate model that might predict dengue fever outbreaks in Bangladesh. The findings revealed that dengue fever is expected to become more frequent in the future. The authors believe that the study findings will be helpful to take early initiatives to combat future dengue outbreaks.

[Diagnostic protocol for febrile syndrome of respiratory origin in geographical areas of endemic risk of tropical infections].

Villamil-Gómez, W.
09-06-2022
Medicine (Madr)
https://doi.org/10.1016/j.med.2022.05.033

The syndromic surveillance of a group of diseases that have similar signs and symptoms, a common pathophysiology, and diverse etiology is aimed at rapidly detecting the presence of outbreaks which could potentially harm public health. This includes not only known outbreaks of infectious origin but also those of unknown origin. In patients suspected of having SARS-CoV-2/COVID-19, it is recommended to consider other etiologies of tropical fever in the differential diagnosis when these patients live in or come from endemic areas, as is the case of dengue, malaria, leptospirosis, acute Chagas disease, and rickettsiosis, among other endemic diseases. The possibility of SARS-CoV-2/AH1 AH5N1 MERS-CoV coinfection with these pathogens should also be considered.

Anti-dengue screening on several Vietnamese medicinal plants: experimental evidences and computational analyses.

Thao, T., Co, N., Anh, H., Luu, N., Hau, V., Thuy, N., Van Chien, T., Anh, N., Bui, T., Cuong, T., Quy, P., Triet, N., Van Sung, T., Nhung, N.
13-06-2022
Chem Biodivers
https://doi.org/10.1002/cbdv.202101026

Worldwide, medicinal plants have been known for economic and geographical advantages, thus possibly holding

potentiality against dengue hemorrhagic fever. The methanol/water extracts from different parts of fourteen Vietnam-based plant species were subjected for experimental screening on anti-dengue activity using baby hamster kidney cells (BHK21) and plaque reduction neutralisation test (PRNT). Firstly, the methanol/water extracts were tested against serotype dengue virus DENV-1. Seven out from nineteen extracts show the PRNT 50 values less than 31.25 µg/mL. Four of the above extracts namely from Euphorbia hirta, Cordyline terminalis, Carica papaya, and Elaeagnus latifolia were chosen for testing against the serotype DENV-2. All of them exhibit good activity with the PRNT 50 values less than 31.25 µg/ml, which were further fractionated to obtain n -hexane, ethyl acetate and n -butanol fractions. Antidengue virus activity of the fractions against four serotypes DENV-1, -2, -3 and -4 was evaluated. As results, the ethyl acetate fraction of Elaeagnus latifolia is highly active against all four serotype viruses. The structural formulae of its nine constituents were input for molecular docking simulation. The docking-based order for static inhibitability is 6-3L6P > 7-3L6P > 9-3L6P > 2-3L6P > 3-3L6P = 5 -3L6P > 9-3L6P > 1-3L6P > 8-3L6P; QSARIS-based analysis reveals the biocompatibility of the most promising ligands (4-7); ADMET-based analysis expects their pharmacological suitability. Exceptional finding on 2-3LKW hydrophilic interaction at Lys43 (with the associated Gibbs free energy of -10.3 kcal.mol -1) raises an open explanation for inhibitory effects. The results encourage further investigations for more in-depth mechanisms and drug development, such as in vitro enzyme assays or in vitro clinical trials with natural substances from E. latifolia .

Deep learning models for forecasting dengue fever based on climate data in Vietnam.

Hau, N., Tuyet Hanh, T., Mulhall, J., Minh, H., Duong, T., Chien, N., Nhung, N., Lan, V., Minh, H., Cuong, D., Bich, N., Quyen, N., Linh, T., Tho, N., Nghia, N., Anh, L., Phan, D., Hung, N., Mai, S.

13-06-2022

PLoS Negl Trop Dis

https://doi.org/10.1371/journal.pntd.0010509

Background: Dengue fever (DF) represents a significant health burden in Vietnam, which is forecast to worsen under climate change. The development of an early-warning system for DF has been selected as a prioritised health adaptation measure to climate change in Vietnam. Objective: This study aimed to develop an accurate DF prediction model in Vietnam using a wide range of meteorological factors as inputs to inform public health responses for outbreak prevention in the context of future climate change. Methods: Convolutional neural network (CNN), Transformer, long short-term memory (LSTM), and attention-enhanced LSTM (LSTM-ATT) models were compared with traditional machine learning models on weather-based DF forecasting. Models were developed using lagged DF incidence and meteorological variables (measures of temperature, humidity, rainfall, evaporation, and sunshine hours) as inputs for 20 provinces throughout Vietnam. Data from 1997-2013 were used to train models, which were then evaluated using data from 2014-2016 by Root Mean Square Error (RMSE) and Mean Absolute Error (MAE). Results and discussion: LSTM-ATT displayed the highest performance, scoring average places of 1.60 for RMSE-based ranking and 1.95 for MAE-based ranking. Notably, it was able to forecast DF incidence better than LSTM in 13 or 14 out of 20 provinces for MAE or RMSE, respectively. Moreover, LSTM-ATT was able to accurately predict DF incidence and outbreak months up to 3 months ahead, though performance dropped slightly compared to short-term forecasts. To the best of our knowledge, this is the first time deep learning methods have been employed for the prediction of both long- and short-term DF incidence and outbreaks in Vietnam using unique, rich meteorological features. Conclusion: This study demonstrates the usefulness of deep learning models for meteorological factor-based DF forecasting. LSTM-ATT should be further explored for mitigation strategies against DF and other climate-sensitive diseases in the coming years.

Risk factors for infection with chikungunya and Zika viruses in southern Puerto Rico: A community-based cross-sectional seroprevalence survey.

Adams, L., Sánchez-González, L., Rodriguez, D., Ryff, K., Major, C., Lorenzi, O., Delorey, M., Medina, F., Muñoz-Jordán, J., Brown, G., Ortiz, M., Waterman, S., Rivera-Amill, V., Paz-Bailey, G.

13-06-2022

PLoS Negl Trop Dis

https://doi.org/10.1371/journal.pntd.0010416

Chikungunya virus (CHIKV) caused a large outbreak in Puerto Rico in 2014, followed by a Zika virus (ZIKV) outbreak in 2016. Communities Organized for the Prevention of Arboviruses (COPA) is a cohort study in southern Puerto Rico, initiated in 2018 to measure arboviral disease risk and provide a platform to evaluate interventions. To identify risk factors for infection, we assessed prevalence of previous CHIKV infection and recent ZIKV and DENV infection in a cross-sectional study among COPA participants. Participants aged 1-50 years (y) were recruited from randomly selected households in study clusters. Each participant completed an interview and provided a blood specimen, which was tested by anti-CHIKV IgG ELISA assay and anti-ZIKV and anti-DENV IgM MAC-ELISA assays. We assessed individual, household, and community factors associated with a positive result for CHIKV or ZIKV after adjusting for confounders. During 2018-2019, 4,090 participants were enrolled; 61% were female and median age was 28y (interquartile range [IQR]: 16-41). Among 4,035 participants tested for CHIKV, 1,268 (31.4%) had evidence of previous infection. CHIKV infection prevalence was lower among children 1-10 years old compared to people 11 and older (adjusted odds ratio [aOR] 2.30; 95% CI 1.71-3.08). Lower CHIKV infection prevalence was associated with home screens (aOR 0.51; 95% CI 0.42-0.61) and air conditioning (aOR 0.64; 95% CI 0.54-0.77). CHIKV infection prevalence also varied by study cluster of residence and insurance type. Few participants (16; 0.4%) had evidence of recent DENV infection by IgM. Among 4,035 participants tested for ZIKV, 651 (16%) had evidence of recent infection. Infection prevalence

increased with older age, from 7% among 1-10y olds up to 19% among 41-50y olds (aOR 3.23; 95% CI 2.16-4.84). Males had an increased risk of Zika infection prevalence compared with females (aOR 1.31; 95% CI 1.09-1.57). ZIKV infection prevalence also decreased with the presence of home screens (aOR 0.66; 95% CI 0.54-0.82) and air conditioning (aOR 0.69; 95% CI 0.57-0.84). Similar infection patterns were observed for recent ZIKV infection prevalence and previous CHIKV infection prevalence by age, and the presence of screens and air conditioners in the home decreased infection risk from both viruses by as much as 50%.

Rapid microfluidic platform for screening and enrichment of cells secreting virus neutralizing antibodies.

Lin, W., Tay, M., Wong, J., Lee, C., Fong, S., Wang, C., Ng, L., Renia, L., Chen, C., Cheow, L.
13-06-2022
Lab Chip
https://doi.org/10.1039/d2lc00018k

As part of the body's immune response, antibodies (Abs) have the ability to neutralize pathogenic viruses to prevent infection. To screen for neutralizing Abs (nAbs) from the immune repertoire, multiple screening techniques have been developed. However, conventional methods have a trade-off between screening throughput and the ability to screen for nAbs *via* their functional efficacy. Although droplet microfluidic platforms have the ability to bridge this disparity, the majority of such reported platforms still rely on Ab-binding assays as a proxy for function, which results in irrelevant hits. Herein, we report the multi-module Droplet-based Platform for Effective Antibody RetrievaL (DROP-PEARL) platform, which can achieve high-throughput enrichment of Ab-secreting cells (ASCs) based on the neutralizing activity of secreted nAbs against the a target virus. In this study, in-droplet Chikungunya virus (CHIKV) infection of host cells and neutralization was demonstrated *via* sequential delivery of viruses and host cells *via* picoinjection. In addition, we demonstrate the ability of the sorting system to accurately discriminate and isolate uninfected droplets from a mixed population of droplets at a rate of 150000 cells per hour. As a proof of concept, a single-cell neutralization assay was performed on two populations of cells (nAb-producing and non-Ab producing cells), and up to 2.75-fold enrichment of ASCs was demonstrated. Finally, we demonstrated that DROP-PEARL is able to achieve similar enrichment for low frequency (~2%) functional nAb-producing cells in a background of excess cells secreting irrelevant antibodies, highlighting its potential prospect as a first round enrichment platform for functional ASCs. We envision that the DROP-PEARL platform could potentially be used to accelerate the discovery of nAbs against other pathogenic viral targets, and we believe it will be a useful in the ongoing fight against biological threats.

Robust control strategy by the Sterile Insect Technique for reducing epidemiological risk in presence of vector migration.

Bliman, P., Dumont, Y.
09-06-2022
Math Biosci
https://pubmed.ncbi.nlm.nih.gov/35691589

The Sterile Insect Technique (SIT) is a promising technique to control mosquitoes, vectors of diseases, like dengue, chikungunya or Zika. However, its application in the field is not easy, and its success hinges upon several constraints, one of them being that the treated area must be sufficiently isolated to limit migration or re-invasion by mosquitoes from the outside. In this manuscript we study the impact of males and (fertile) females migration on SIT. We show that a critical release rate for sterile males exists for every migration level, in the context of continuous or periodic releases. In particular, when (fertile) females migration is sufficiently low, then SIT can be conducted successfully using either open-loop control or closed-loop control (or a combination of both methods) when regular measurements of the wild population are completed. Numerical simulations to illustrate our theoretical results are presented and discussed. Finally, we derive a threshold value for the females migration rate, when viruses are circulating, under which it is possible to lower the epidemiological risk in the treated area, according to the size of the human population.

Maternal and foetal-neonatal outcomes of dengue virus infection during pregnancy.

Revue de littérature

Rathore, S., Oberoi, S., Hilliard, J., Raja, R., Ahmed, N., Vishwakarma, Y., Iqbal, K., Kumari, C., Velasquez-Botero, F., Nieto-Salazar, M., Cortes, G., Akomaning, E., Musa, I.
11-06-2022
Trop Med Int Health
https://doi.org/10.1111/tmi.13783

Objective: Given that women of reproductive age in dengue-endemic areas are at risk of infection, it is necessary to determine whether dengue virus (DENV) infection during pregnancy is associated with adverse outcomes. The aim of this systematic review and meta-analysis is to investigate the consequences of DENV infection in pregnancy on various maternal and foetal-neonatal outcomes. **Methods:** A systematic literature search was undertaken using PubMed, Google Scholar, and Embase till December 2021. Mantel-Haenszel risk ratios were calculated to report overall effect size using random effect models. The pooled prevalence was computed using the random effect model. All statistical analyses were performed on MedCalc Software. **Result:** We obtained data from 36 studies involving 39,632 DENV-infected pregnant women. DENV infection in pregnancy was associated with an increased risk of maternal mortality (OR = 4.14 [95% CI, 1.17-14.73]), stillbirth (OR = 2.71 [95% CI, 1.44-5.10]), and neonatal deaths (OR = 3.03 [95% CI, 1.17-7.83]) compared with pregnant women without DENV infection. There was no significant statistical association established between

maternal DENV infection and the outcomes of preterm birth, maternal bleeding, low birth weight in neonates, and risk of miscarriage. Pooled prevalences were 14.9% for dengue shock syndrome, 14% for preterm birth, 13.8% for maternal bleeding, 10.1% for low birth weight, 6% for miscarriages, and 5.6% for stillbirth. Conclusion: DENV infection in pregnant women may be associated with adverse outcomes such as maternal mortality, stillbirth, and neonatal mortality. Hence, pregnant women should be considered an at-risk population for dengue management programmes.

Surveillance for Zika, chikungunya and dengue virus incidence and RNAemia in blood donors at four Brazilian blood centers during 2016-2019.

Custer, B., Grebe, E., Buccheri, R., Bakkour, S., Stone, M., Capuani, L., Alencar, C., Amorim, L., Loureiro, P., Carneiro-Proietti, A., Mendrone-Junior, A., Gonçalez, T., Gao, K., Livezey, K., Linnen, J., Brambilla, D., McClure, C., Busch, M., Sabino, E., Recipient Epidemiology and Donor Evaluation Study (REDS-III) International Component Brazil
11-06-2022
J Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35687888

Background: Except for public health case reports, the incidence of Zika virus (ZIKV), chikungunya virus (CHIKV) and dengue virus (DENV) infection are not available to assess the potential blood transfusion safety threat in Brazil. Methods: Pools of 6 donation samples (MP6) left over from HIV, HBV, and HCV nucleic acid testing were combined to create MP18 pools (3 MP6 pools). Samples were tested using the Grifols triplex ZIKV, CHIKV and DENV real-time transcription mediated amplification assay to estimate prevalence of RNAemia, incidence, and to compare these results to case reports in São Paulo, Belo Horizonte, Recife and Rio de Janeiro, from April 2016 - June 2019. Results: ZIKV, CHIKV and DENV RNAemia were found from donors who donated without overt symptoms of infection that would have led to deferral. The highest RNAemic donation prevalence was (1.2%, 95% CI 0.8-1.9) for DENV in Belo Horizonte in May 2019. Arbovirus infections varied by location, time of year, and were not always aligned with annual arbovirus outbreak seasons in different regions of the country. Conclusions: Testing donations for arboviruses in Brazil can contribute to public health. Transfusion recipients were likely exposed to ZIKV, CHIKV, DENV viremic blood components during the study period.

Increased Repellent Effect of DEET on Aedes aegypti (Diptera: Culicidae) Field Population.

Maia, P., La Corte, R., Pires, L., Banfield, L., Logan, J., Lima-Camara, T.
10-06-2022
J Med Entomol
https://pubmed.ncbi.nlm.nih.gov/35686335

Insecticides and repellents are routinely used in Brazil because of the high rates of arbovirus transmission and the nuisance caused by mosquitoes. However, few studies have assessed the effectiveness of repellents against mosquito populations that have been under exposure to xenobiotics, mainly insecticides and repellents. This study investigated the sensitivity of a field population of Aedes aegypti (Linnaeus, 1762) from a dengue-endemic area under high insecticide pressure to N,N-diethylmethylbenzamide (DEET), the active ingredient in common repellent products. The field (Laranjeiras, Sergipe, Brazil) and laboratory (Rockefeller) populations were characterized for the presence of the Val1016Ile kdr mutation, associated with pyrethroid resistance, and locomotor activity. Repellency bioassays were performed to assess the response of the mosquitoes to human odor by exposing them to 10% DEET applied to the skin in ethanol. Samples from the field population showed higher frequency of the kdr mutation, 21.9% homozygous and 21.9% heterozygous, greater locomotor activity and greater sensitivity to DEET than the laboratory population. These results suggest increased sensitivity to DEET in field populations and a possible interaction between insecticide exposure and sensitivity to DEET.

MicroRNAs and other small RNAs in Aedes aegypti saliva and salivary glands following chikungunya virus infection.

Fiorillo, C., Yen, P., Colantoni, A., Mariconti, M., Azevedo, N., Lombardo, F., Failloux, A., Arcà, B.
09-06-2022
Sci Rep
https://doi.org/10.1038/s41598-022-13780-3

Mosquito saliva facilitates blood feeding through the anti-haemostatic, anti-inflammatory and immunomodulatory properties of its proteins. However, the potential contribution of non-coding RNAs to host manipulation is still poorly understood. We analysed small RNAs from Aedes aegypti saliva and salivary glands and show here that chikungunya virus-infection triggers both the siRNA and piRNA antiviral pathways with limited effects on miRNA expression profiles. Saliva appears enriched in specific miRNA subsets and its miRNA content is well conserved among mosquitoes and ticks, clearly pointing to a non-random sorting and occurrence. Finally, we provide evidence that miRNAs from Ae. aegypti saliva may target human immune and inflammatory pathways, as indicated by prediction analysis and searching for experimentally validated targets of identical human miRNAs. Overall, we believe these observations convincingly support a scenario where both proteins and miRNAs from mosquito saliva are injected into vertebrates during blood feeding and contribute to the complex vector-host-pathogen interactions.

Immunomodulatory therapy in dengue: need for clinical trials and evidence base.

Bhat, C., Shetty, R., Sundaram, B., Ramanan, A.
09-06-2022
Arch Dis Child
https://pubmed.ncbi.nlm.nih.gov/35680407

The Aedes aegypti siRNA pathway mediates broad-spectrum defense against human pathogenic viruses and modulates antibacterial and antifungal defenses.

Dong, Y., Dong, S., Dizaji, N., Rutkowski, N., Pohlenz, T., Myles, K., Dimopoulos, G.
09-06-2022
PLoS Biol
https://doi.org/10.1371/journal.pbio.3001668

The mosquito's innate immune system defends against a variety of pathogens, and the conserved siRNA pathway plays a central role in the control of viral infections. Here, we show that transgenic overexpression of Dicer2 (Dcr2) or R2d2 resulted in an accumulation of 21-nucleotide viral sequences that was accompanied by a significant suppression of dengue virus (DENV), Zika virus (ZIKV), and chikungunya virus (CHIKV) replication, thus indicating the broad-spectrum antiviral response mediated by the siRNA pathway that can be applied for the development of novel arbovirus control strategies. Interestingly, overexpression of Dcr2 or R2d2 regulated the mRNA abundance of a variety of antimicrobial immune genes, pointing to additional functions of DCR2 and R2D2 as well as cross-talk between the siRNA pathway and other immune pathways. Accordingly, transgenic overexpression of Dcr2 or R2d2 resulted in a lesser proliferation of the midgut microbiota and increased resistance to bacterial and fungal infections.

Faster indicators of chikungunya incidence using Google searches.

Miller, S., Preis, T., Mizzi, G., Bastos, L., Gomes, M., Coelho, F., Codeço, C., Moat, H.
09-06-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010441

Chikungunya, a mosquito-borne disease, is a growing threat in Brazil, where over 640,000 cases have been reported since 2017. However, there are often long delays between diagnoses of chikungunya cases and their entry in the national monitoring system, leaving policymakers without the up-to-date case count statistics they need. In contrast, weekly data on Google searches for chikungunya is available with no delay. Here, we analyse whether Google search data can help improve rapid estimates of chikungunya case counts in Rio de Janeiro, Brazil. We build on a Bayesian approach suitable for data that is subject to long and varied delays, and find that including Google search data reduces both model error and uncertainty. These improvements are largest during epidemics, which are particularly important periods for policymakers. Including Google search data in chikungunya surveillance systems may therefore help policymakers respond to future epidemics more quickly.

Lipases secreted by a gut bacterium inhibit arbovirus transmission in mosquitoes.

Yu, X., Tong, L., Zhang, L., Yang, Y., Xiao, X., Zhu, Y., Wang, P., Cheng, G.
09-06-2022
PLoS Pathog
https://doi.org/10.1371/journal.ppat.1010552

Arboviruses are etiological agents of various severe human diseases that place a tremendous burden on global public health and the economy; compounding this issue is the fact that effective prophylactics and therapeutics are lacking for most arboviruses. Herein, we identified 2 bacterial lipases secreted by a Chromobacterium bacterium isolated from Aedes aegypti midgut, Chromobacterium antiviral effector-1 (CbAE-1) and CbAE-2, with broad-spectrum virucidal activity against mosquito-borne viruses, such as dengue virus (DENV), Zika virus (ZIKV), Japanese encephalitis virus (JEV), yellow fever virus (YFV) and Sindbis virus (SINV). The CbAEs potently blocked viral infection in the extracellular milieu through their lipase activity. Mechanistic studies showed that this lipase activity directly disrupted the viral envelope structure, thus inactivating infectivity. A mutation in the lipase motif of CbAE-1 fully abrogated the virucidal ability. Furthermore, CbAEs also exert lipase-dependent entomopathogenic activity in mosquitoes. The anti-arboviral and entomopathogenic properties of CbAEs render them potential candidates for the development of novel transmission control strategies against vector-borne diseases.

Dengue fever presenting as acute cerebellar ataxia: Case report and literature review.

de Holanda, A., Maranhão, E., Van Der Linden Ferreira Silva, L., Bezerra, M., de Melo, E.
09-06-2022
J Neurovirol
https://doi.org/10.1007/s13365-022-01082-3

Dengue fever has been associated with several neurological complications, cerebellar involvement being among the rarest of them. Here, we describe the case of a 70-year-old female who presented a cerebellar syndrome during the first day of an arboviral infection, posteriorly confirmed as dengue fever. Among the seven other cases in which the relationship between dengue virus and ataxia was reported, only in one cerebellar presentation occurred as early. Onset, course, and prognosis, as well as the adequate investigation and management of these patients, are discussed. While the disease pattern is not better characterized by future studies, differential diagnosis and close follow-up are essential tools for guaranteeing good outcomes.

Vaccine-induced antibodies to contemporary strains of dengue virus type 4 show a mechanistic correlate of protective immunity.

Gallichotte, E., Henein, S., Nivarthi, U., Delacruz, M., Scobey, T., Bonaparte, M., Moser, J., Munteanu, A., Baric, R., de Silva, A.
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Cell Rep
https://pubmed.ncbi.nlm.nih.gov/35675766

The four dengue virus serotypes (DENV1-4) are mosquito-borne flaviviruses of humans. Several live-attenuated tetravalent DENV vaccines are at different stages of clinical development and approval. In children with no baseline immunity to DENVs, a leading vaccine (Dengvaxia) is efficacious against vaccine-matched DENV4 genotype II (GII) strains but not vaccine-mismatched DENV4 GI viruses. We use a panel of recombinant DENV4 viruses displaying GI or GII envelope (E) proteins to map Dengvaxia-induced neutralizing antibodies (NAbs) linked to protection. The vaccine stimulated antibodies that neutralize the DENV4 GII virus better than the GI virus. The neutralization differences map to 5 variable amino acids on the E protein located within a region targeted by DENV4 NAbs, supporting a mechanistic role for these epitope-specific NAbs in protection. In children with no baseline immunity to DENVs, levels of DENV4 serotype- and genotype-specific NAbs induced by vaccination are predictive of vaccine efficacy.

Impacts of El Niño Southern Oscillation on the dengue transmission dynamics in the Metropolitan Region of Recife, Brazil.

Ferreira, H., Nóbrega, R., Brito, P., Farias, J., Amorim, J., Moreira, E., Mendez, É., Luiz, W.
06-06-2022
Rev Soc Bras Med Trop
https://pubmed.ncbi.nlm.nih.gov/35674563

Background: This research addresses two questions: (1) how El Niño Southern Oscillation (ENSO) affects climate variability and how it influences dengue transmission in the Metropolitan Region of Recife (MRR), and (2) whether the epidemic in MRR municipalities has any connection and synchronicity. Methods: Wavelet analysis and cross-correlation were applied to characterize seasonality, multiyear cycles, and relative delays between the series. This study was developed into two distinct periods. Initially, we performed periodic dengue incidence and intercity epidemic synchronism analyses from 2001 to 2017. We then defined the period from 2001 to 2016 to analyze the periodicity of climatic variables and their coherence with dengue incidence. Results: Our results showed systematic cycles of 3-4 years with a recent shortening trend of 2-3 years. Climatic variability, such as positive anomalous temperatures and reduced rainfall due to changes in sea surface temperature (SST), is partially linked to the changing epidemiology of the disease, as this condition provides suitable environments for the Aedes aegypti lifecycle. Conclusion: ENSO may have influenced the dengue temporal patterns in the MRR, transiently reducing its main way of multiyear variability (3-4 years) to 2-3 years. Furthermore, when the epidemic coincided with El Niño years, it spread regionally and was highly synchronized.

A System for Structuring, Storage and Georeferenciation of Dengue Vector Surveillance Data.

Conrado, D., Dos Santos, V., Faria-Campos, A., Serufo, J., Campos, S.
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Stud Health Technol Inform
https://doi.org/10.3233/SHTI220064

Dengue is a main public health issue around the world and is an epidemic in Brazil. As part of the Brazilian national program to fight the disease, every municipality has a Zoonosis Control Center responsible for health and case surveillance, among other actions. The fieldwork includes routine visiting of houses and strategic sites (e.g. industries and vacant lands), water sampling, container elimination, and larvicide administration. However, the field data are gathered and summarized by hand. In this work, our goal is to ease the collection and visualization of field data to support decision-making. We have developed a mobile system to collect and georeference field data which could then be used to build geospatial and geo-temporal visualizations of indices such as House, Container, and Breteau1 indices. This solution could enhance entomological surveillance and leverage action planning and evaluation.

Dengue infection triggered immune mediated necrotizing myopathy in children: a case report and literature review.

Revue de littérature

Mekmangkonthong, A., Amornvit, J., Numkarunarunrote, N., Veeravigrom, M., Khaosut, P.
07-06-2022
Pediatr Rheumatol Online J
https://doi.org/10.1186/s12969-022-00699-2

Background: Immune-mediated necrotizing myopathy (IMNM) is a subgroup of idiopathic inflammatory myopathies manifesting with progressive weakness, elevated serum creatine kinase (CK) levels, and necrotizing myopathic features on muscle biopsy. There is a paucity of data on the clinical presentation of IMNM in children. We report a paediatric patient who developed anti-3-hydroxy-3-methylglutaryl-CoA reductase (anti-HMGCR)-positive necrotizing myopathy after recent dengue infection. Case presentation: A previously healthy 9-year-old boy presented with acute proximal muscle weakness after recovery from dengue infection. Five days after the fever subsided, he could not stand from a squatting position. He denied having skin rash, arthritis, or other systemic features. He had marked elevation of CK level of 30,833 mg/dL and was put on steroid therapy. The patient initially responded to oral prednisolone, however the weakness persisted and muscle enzymes increased as steroids were decreased. He was then referred to our hospital for further assessment. Subsequent investigation revealed anti-HMGCR positivity along with specific histopathological findings consistent with IMNM. The patient was treated with six cycles of intravenous immunoglobulin (IVIG) monthly, then followed by a gradual taper of prednisolone and oral methotrexate weekly with complete recovery in motor power. Conclusions: Our report presents a child with clinical manifestations of IMNM which can be categorized as acute onset of muscle

weakness following dengue infection. Two key points supporting a diagnosis in this case are clinical response after immunosuppressive therapy and absence of rashes found in juvenile dermatomyositis.

[Important arboviral diseases in returning travelers: dengue, chikungunya and zika].

Niederfahrenhorst, A., Rothe, C.
07-06-2022
Dtsch Med Wochenschr
https://doi.org/10.1055/a-1661-3847

Arboviral infections are an important differential diagnosis in returning travelers with fever, muscle or joint pain and rash. Arboviruses have spread widely around the globe in the last decades. The most common arboviral infections in returning travelers from tropical and subtropical areas are dengue, chikungunya and zika. Their most important vectors, Aedes (Stegomyia) mosquito species, have adapted to the urban environment, which enabled arboviruses to establish urban transmission cycles. Population growth, urbanization, globalization, modern means of transportation and global warming are speeding up their spread.Laboratory confirmation of an arboviral infection can generally be obtained by direct virus detection (PCR, antigen test) in the first week of illness; from the second week of illness serology can be used. Treatment is mostly symptomatic.Dengue fever is the most common cause of fever in returning travelers from South-East Asia. Patients have to be educated about and observed for warning signs of severe dengue that can rarely develop around day 5 of the disease and is marked by a rise in hematocrit.Chikungunya mostly occurs in epidemics and is characterized by severe and often long-lasting arthritis.Preconceptional screening for zika virus infection is not recommended. Instead, travelers should delay conception for up to three months after returning from a zika endemic area.Dengue, chikungunya and zika vaccine development has been hampered by difficulties, for example antibody-dependent-enhancement or the unpredictability of outbreaks, and up to now no vaccines for travelers have been licensed. Yet several promising vaccine candidates are currently under development.

Somatic Hypermutation and Framework Mutations of Variable Region Contribute to Anti-Zika Virus-Specific Monoclonal Antibody Binding and Function.

Tsuji, I., Vang, F., Dominguez, D., Karwal, L., Sanjali, A., Livengood, J., Davidson, E., Fouch, M., Doranz, B., Das, S., Dean, H.
16-05-2022
J Virol
https://doi.org/10.1128/jvi.00071-22

Zika virus (ZIKV) is a global public health concern due to its ability to cause congenital Zika syndrome and lack of approved vaccine, therapeutic, or other control measures. We discovered eight novel rabbit monoclonal antibodies (MAbs) that bind to distinct ZIKV envelope protein epitopes. The majority of the MAbs were ZIKV specific and targeted the lateral ridge of the envelope (E) protein domain III, while the MAb with the highest neutralizing activity recognized a putative quaternary epitope spanning E protein domains I and III. One of the non-neutralizing MAbs specifically recognized ZIKV precursor membrane protein (prM). Somatic hypermutation of immunoglobulin variable regions increases antibody affinity maturation and triggers antibody class switching. Negative correlations were observed between the somatic hypermutation rate of the immunoglobulin heavy-chain variable region and antibody binding parameters such as equilibrium dissociation constant, dissociation constant, and half-maximal effective concentration value of MAb binding to ZIKV virus-like particles. Complementarity-determining regions recognize the antigen epitopes and are scaffolded by canonical framework regions. Reversion of framework region amino acids to the rabbit germ line sequence decreased anti-ZIKV MAb binding activity of some MAbs. Thus, antibody affinity maturation, including somatic hypermutation and framework region mutations, contributed to the binding and function of these anti-ZIKV MAbs. **IMPORTANCE** ZIKV is a global health concern against which no vaccine or therapeutics are available. We characterized eight novel rabbit monoclonal antibodies recognizing ZIKV envelope and prM proteins and studied the relationship between somatic hypermutation of complementarity-determining regions, framework regions, mutations, antibody specificity, binding, and neutralizing activity. The results contribute to understanding structural features and somatic mutation pathways by which potent Zika virus-neutralizing antibodies can evolve, including the role of antibody framework regions.

The innate immune response following multivalent dengue vaccination and implications for protection against dengue challenge.

Hou, R., Tomalin, L., Silva, J., Kim-Schulze, S., Whitehead, S., Fernandez-Sesma, A., Durbin, A., Suárez-Fariñas, M.
08-06-2022
JCI Insight
https://doi.org/10.1172/jci.insight.157811

Understanding the immune response to dengue virus (DENV) is essential for developing a dengue vaccine that is protective against all 4 DENV serotypes. We evaluated the immune response after vaccination (live attenuated tetravalent dengue vaccine TV005 or trivalent admixture) and after challenge with DEN2Δ30 (Tonga/74) to better understand the importance of homotypic immunity in vaccine protection. Significant increases in IP-10 expression were observed following receipt of either the trivalent or tetravalent vaccine. After challenge, a large increase in IP-10 expression was observed in the placebo and trivalent admixture groups but not in the tetravalent vaccine group. MCP-1, IL-1RA, and MIP-1β exhibited a similar pattern as IP-10. These results demonstrate protective effects of trivalent and tetravalent vaccines against DENV and suggest that the tetravalent vaccine has a better protective effect

compared with the trivalent admixture. We also explored the postvaccination and postchallenge immune response differences between Black and White participants. White participants responded to vaccine differently than Black participants; Black participants receiving trivalent and tetravalent vaccines responded strongly and White participants responded only transiently in trivalent group. In response to challenge, White participants elicited a stronger response than Black participants. These results may explain why White participants may have a more vigorous DENV immune response than Black participants, as reported in literature.

Fever in the Returning Traveler.

Paquet, D., Jung, L., Trawinski, H., Wendt, S., Lübbert, C.
07-06-2022
Dtsch Arztebl Int
https://doi.org/10.3238/arztebl.m2022.0182

Background: It is predicted that approximately two billion tourist trips to foreign countries will be taken worldwide each year by 2030. Germany has long been among the most active countries in tourism. The frequency of illness among persons returning from developing and newly industrialized countries is 43-79%. The appropriate diagnosis of fever in returning travelers is a clinically important matter, as it can be a sign of a life-threatening illness. Methods: This review is based on publications (2001-2022) retrieved by a selective search in PubMed for studies on the epidemiology, diagnosis, and treatment of febrile illnesses in returning travelers, or on specific tropical diseases. Results: Diarrhea, fever, and skin changes are the most common manifestations of disease after travel to tropical and subtropical areas. The diagnostic evaluation should be performed in a series of steps, beginning with a precise travel history and the identification of specific risk factors. Among travelers returning from sub-Saharan Africa, Plasmodium falciparum malaria is the most common cause of fever on presentation to centers for infectious diseases and tropical medicine, affecting approximately 50 per 1000 travelers. Among persons returning from travel to Southeast Asia, dengue fever is the most common infectious disease, affecting 50-160 per 1000 travelers. Further potentially dangerous diseases include chikungunya and zika fever, typhoid and paratyphoid fever, amoebic liver abscess, visceral leishmaniasis (kala-azar), leptospirosis, and, very rarely, imported cases of viral hemorrhagic fever. COVID-19 and influenza are important differential diagnoses. Conclusion: The differential diagnosis can be narrowed by thorough history-taking with particular attention to the patient's travel route, combined with a good knowledge of the geographic spread and incubation times of the main tropical diseases. Algorithms help clinicians to focus the diagnostic work-up and select the appropriate further laboratory tests and diagnostic procedures.

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

Alves Rubio, F., Mo Yang, H.
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Math Med Biol
https://doi.org/10.1093/imammb/dqab021

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

RAGE

Robust humoral immune response against rabies virus in rabbits and Guinea pigs immunized with plasmid DNA vectors encoding rabies virus glycoproteins - An approach to the production of polyclonal antibody reagents.

Volokhov, D., Furtak, V., Allen, C., Pulle, G., Zajac, M., Levin, Y., Kochba, E., Moore, S.
09-06-2022
Mol Cell Probes
https://pubmed.ncbi.nlm.nih.gov/35691598

DNA-based immunization has been previously shown to be an efficient approach to induce robust immunity against infectious diseases in animals and humans. The advantages of DNA vaccines are simplicity of their construction and production, low cost, high stability, and ability to elicit a full spectrum of immune responses to target antigens. The goals of this study were (i) to assess the antibody immune response to rabies virus glycoproteins (rGPs) in rabbits and guinea pigs after intramuscular immunization with pTargeT and pVAC2-mcs mammalian expression vectors encoding either the wild-type (WT) or codon-optimized (cOPT) rGP genes; and (ii) to prepare in-house rabbit anti-rGP polyclonal antibody reagents suitable for in Single Radial Immunodiffusion (SRID) and Indirect Fluorescent Antibody (IFA) assays. The maximum antibody responses against rabies virus in rabbits and guinea pigs were observed after immunization series with 500 µg/dose of pVAC2-mcs vector encoding either the WT or cOPT rGP genes adjuvanted with Emulsigen-D. No significant difference in the anti-rabies virus neutralizing antibody titers

was observed in rabbits immunized with the WT and cOPT rGPs. The in-house rabbit anti-rGP polyclonal antibody reagents reacted comparable to the current reference reagents in SRID and IFA assays. The results of the study demonstrated that the DNA immunization of animals with the WT or cOPT rGPs is a promising approach to either induction of high anti-rabies virus neutralizing antibody titers in vivo or for production of polyclonal antibody reagents against rabies.

Establishment of a Captive Cave Nectar Bat (Eonycteris spelaea) Breeding Colony in Singapore.

Foo, R., Hey, Y., Jia, J., Chionh, Y., Chia, W., Kong, P., Lee, B., Kang, A., Borthwick, S., Low, D., Mendenhall, I., Pena, E., Yroy, R., Ng, B., Wang, L.
10-06-2022
J Am Assoc Lab Anim Sci
https://doi.org/10.30802/AALAS-JAALAS-21-000090

Bats are known natural reservoirs of several highly pathogenic zoonotic viruses, including Hendra virus, Nipah virus, rabies virus, SARS-like coronaviruses, and suspected ancestral reservoirs of SARS-CoV-2 responsible for the ongoing COVID-19 pandemic. The capacity to survive infections of highly pathogenic agents without severe disease, together with many other unique features, makes bats an ideal animal model for studying the regulation of infection, cancer, and longevity, which is likely to translate into human health outcomes. A key factor that limits bat research is lack of breeding bat colonies. To address this need, a captive bat colony was established in Singapore from 19 wild-caught local cave nectar bats. The bats were screened for specific pathogens before the start of captive breeding. Custom-made cages and an optimized diet inclusive of Wombaroo dietary formula, liquid diet, and supplement of fruits enabled the bats to breed prolifically in our facility. Cages are washed daily and disinfected once every fortnight. Bats are observed daily to detect any sick bat or abnormal behavior. In addition, bats undergo a thorough health check once every 3 to 4 mo to check on their overall wellbeing, perform sampling, and document any potential pregnancy. The current colony houses over 80 bats that are successfully breeding, providing a valuable resource for research in Singapore and overseas.

Safety and clinical efficacy of human rabies immunoglobulin in post exposure prophylaxis for category III animal exposures.

Haradanhalli, R., Fotedar, N., Kumari, N., Narayana, D.
10-06-2022
Hum Vaccin Immunother
https://doi.org/10.1080/21645515.2022.2081024

The human rabies immunoglobulin (HRIG) is a life-saving immune biological essential for all category III animal exposures. It provides neutralizing antibodies at the site of exposure until the body can produce vaccine-mediated antibodies. We conducted this study to determine the safety and clinical efficacy of an HRIG being used presently for post-exposure prophylaxis (PEP) and to strengthen the existing evidence for its further usage. We conducted a prospective cohort study in 123 subjects with category III animal exposures at the KIMS Hospital and Research Center, Bangalore, India. Post-exposure prophylaxis (PEP) with wound toilet, a single application of HRIG, and a full course of anti-rabies vaccination were provided to all the study subjects. The volume of HRIG was calculated according to the body weight, and all the wounds were infiltrated as was anatomically feasible. All the study subjects were followed up for immediate and delayed adverse events (AE), both local and systemic. Subsequently, all the subjects were followed up for 6 months to demonstrate the clinical efficacy of PEP. The incidence of AEs was 11.4% including local pain, erythema, itching, headache, body ache, fever, and malaise. All AEs were mild and subsided without any complications. All the study subjects were healthy and alive after 6 months following the administration of HRIG, along with a full course of anti-rabies vaccine. Our study provides evidence of safety and clinical efficacy of HRIG for category III animal exposures and supports its continued usage.

Experiences in Using KoBo Collect and KoBo Toolbox in a Cross-Sectional Dog Population and Rabies Knowledge and Practices Household Survey in the Philippines.

Dizon, T., Saito, N., Reñosa, M., Bravo, T., Silvestre, C., Endoma, V., Guevarra, J., Quiambao, B., Nishizono, A.
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Stud Health Technol Inform
https://doi.org/10.3233/SHTI220278

We used KoBo Collect and KoBo Toolbox as an electronic data capture platform for a dog population and rabies knowledge and practices community survey in the Philippines. It has allowed for easy design and deployment of an electronic form with minimal technical knowledge from the investigators. Using this platform allowed for shorter training for data collectors, minimal errors during data collection, and faster turn-around time for data cleaning and analysis.

A cocktail of human monoclonal antibodies broadly neutralizes North American rabies virus variants as a promising candidate for rabies post-exposure prophylaxis.

Ejemel, M., Smith, T., Greenberg, L., Carson, W., Lowe, D., Yang, Y., Jackson, F., Morgan, C., Martin, B., Kling, C., Hutson, C., Gallardo-Romero, N., Ellison, J., Moore, S., Buzby, A., Sullivan-Bolyai, J., Klempner, M., Wang, Y.
07-06-2022
Sci Rep
https://doi.org/10.1038/s41598-022-13527-0

Human rabies remains a globally significant public health problem. Replacement of polyclonal anti-rabies immunoglobulin (RIG), a passive component of rabies post-exposure prophylaxis (PEP), with a monoclonal antibody

(MAb), would eliminate the cost and availability constraints associated with RIG. Our team has developed and licensed a human monoclonal antibody RAB1 (Rabishield©), as the replacement for RIG where canine rabies is enzootic. However, for the highly diverse rabies viruses of North America, a cocktail containing two or more MAbs targeting different antigenic sites of the rabies glycoprotein should be included to ensure neutralization of all variants of the virus. In this study, two MAb cocktails, R172 (RAB1-RAB2) and R173 (RAB1-CR57), were identified and evaluated against a broad range of rabies variants from North America. R173 was found to be the most potent cocktail, as it neutralized all the tested North American RABV isolates and demonstrated broad coverage of isolates from both terrestrial and bat species. R173 could be a promising candidate as an alternative or replacement for RIG PEP in North America.

TRACHOME

ULCERE DE BURULI

PIAN

LEPRE

Association of CD209 (DC-SIGN) rs735240 SNV with paucibacillary leprosy in the Brazilian population and its functional effects.

Germano, G., Braga, A., Camargo, R., Ballalai, P., Bezerra, O., Manta, F., Belone, A., Soares, C., Das, P., Moraes, M., Latini, A., Brito de Souza, V.
10-06-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35703715

Background: Leprosy, caused by Mycobacterium leprae, is a public health problem in Brazil that affects peripheral nerves, resulting in physical disabilities. During host-pathogen interactions, the immune response determines leprosy outcomes from a localised (paucibacillary) form to a disseminated (multibacillary) form. The recognition of M. leprae involves the DC-SIGN receptor, which is present on the dendritic cells (DCs) and participates in immune activation. Objectives: To evaluate the association of polymorphisms in the promoter region of the gene encoding DC-SIGN (CD209) and the clinical form of leprosy, and to investigate its functional effects. Methods: The study population included 406 leprosy patients from an endemic area in Brazil [310 multibacillary (MB); 96 paucibacillary (PB)]. A functional evaluation based on the effects of the single nucleotide variant (SNV) associated with PB leprosy on the specific immune response was also performed. Results: The GA genotype and the presence of the A allele of rs735240 (-939G>A) were associated with PB leprosy [OR: 2.09 (1.18-3.69) and 1.84 (1.07-3.14), respectively]. Carriers of the A allele showed reduced expression of CD209 and TGF-β1 in leprosy lesions in comparison with individuals with GG genotype, in addition to a higher response to the Mitsuda test. Conclusion: These data suggest that rs735240 influences the immune response against M. leprae and clinical presentation of leprosy.

The Awesome Power of Human Genetics of Infectious Disease.

Revue de littérature

Gibbs, K., Schott, B., Ko, D.
13-06-2022
Annu Rev Genet
https://doi.org/10.1146/annurev-genet-080320-010449

Since the identification of sickle cell trait as a heritable form of resistance to malaria, candidate gene studies, linkage analysis paired with sequencing, and genome-wide association (GWA) studies have revealed many examples of genetic resistance and susceptibility to infectious diseases. GWA studies enabled the identification of many common variants associated with small shifts in susceptibility to infectious diseases. This is exemplified by multiple loci associated with leprosy, malaria, HIV, tuberculosis, and coronavirus disease 2019 (COVID-19), which illuminate genetic architecture and implicate pathways underlying pathophysiology. Despite these successes, most of the heritability of infectious diseases remains to be explained. As the field advances, current limitations may be overcome by applying methodological innovations such as cellular GWA studies and phenome-wide association (PheWA) studies as well as by improving methodological rigor with more precise case definitions, deeper phenotyping, increased cohort diversity, and functional validation of candidate loci in the laboratory or human challenge studies. Expected final online publication date for the *Annual Review of Genetics*, Volume 56 is November 2022. Please see http://www.annualreviews.org/page/journal/pubdates for revised estimates.

Understanding leprosy reactions and the impact on the lives of people affected: An exploration in two leprosy endemic countries.

Putri, A., de Sabbata, K., Agusni, R., Alinda, M., Darlong, J., de

Barros, B., Walker, S., Zweekhorst, M., Peters, R.
13-06-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010476

Background: Leprosy reactions, Type-1 and erythema nodosum leprosum, are immune-mediated complications of leprosy, which play a significant role in the morbidity associated with the disease. A considerable amount of literature has been published on the impact of leprosy in general but few studies focus specifically on leprosy reactions. This study aimed to investigate the impact of leprosy reactions on physical, psychological, and social aspects of the lives of people affected by analysing their life experiences and perspectives about leprosy reactions. **Methods/Principal findings:** This qualitative study involved people affected by leprosy reactions and their family members in two leprosy endemic countries. The data were collected through 66 interviews and 9 focus group discussions (4-6 participants each) in Surabaya, Indonesia, and Purulia, India. Content analysis and conversational analysis were performed. This study found that both types of leprosy reactions were perceived as an unpredictable and painful condition. Leprosy reactions restricted physical activities of the participants, such as going to bathroom, sleeping, eating, and cooking. In the interviews, the respondents expressed a range of emotions and feelings including confusion, sadness, anxiety, and anger. Some recounted that they felt stigmatized and lost opportunities to socialise and earn money. Differences between the two settings were identified. The majority of Indonesian participants preferred to stay at home, and some concealed the diagnosis of leprosy, while most of the Indian respondents continued working up to the time of hospitalization. **Conclusion:** Leprosy reactions are a distressing complication of leprosy and adversely affect the lives of those affected. Individuals reported physical discomfort, distress, anxiety, stigma, and financial hardship and these negative impacts in the physical, psychological, and social spheres reinforced each other. These findings provide important information about a need for early detection and sustained commitment to follow-up care for people with a history of leprosy reactions. More research on new drugs for reactional episodes, tools to measure knowledge, attitude, and practice, and costing study on leprosy reactions treatment are needed. We recommend the development and testing of holistic strategies to improve the management of leprosy reactions.

Are the clinical features of leprosy and American tegumentary leishmaniasis worse in patients with both diseases?

Carvalho, A., Luz, J., Steinmann, P., Ignotti, E.
06-06-2022
Rev Inst Med Trop Sao Paulo
https://pubmed.ncbi.nlm.nih.gov/35674635

This cross-sectional population-based study compared clinical features of leprosy and American tegumentary leishmaniasis (ATL) in patients diagnosed with both diseases (n=414) and in those diagnosed with only leprosy (n=27,790) or only ATL (n=24,357) in Mato Grosso State, which is a hyperendemic area for both diseases in Midwest Brazil. All new cases of leprosy and ATL reported in the area from 2008 to 2017 were included. Patients diagnosed with both diseases were identified by a probabilistic linkage procedure applied to leprosy and ATL databases of the national reporting system. The distribution of the frequency of clinical features between groups was compared by the chi-square test, followed by a multivariate logistic regression. Patients diagnosed with both leprosy and ATL presented higher odds of having nerve damage (OR: 1.34; 95% CI: 1.09-1.66) and leprosy reactions (OR: 1.35; 95% CI: 1.04-1.76) compared to patients diagnosed only with leprosy. Mucocutaneous leishmaniasis (OR: 2.29; 95% CI: 1.74-3.00) was more frequent among patients with both diagnoses when compared to patients who only had ATL. In conclusion, patients diagnosed with both leprosy and ATL present more severe clinical features of such diseases. Our data can be useful for designing health policies aimed at timely and integrated management of leprosy and ATL in co-endemic areas.

TRYPANOSOMES (TRYPANOSOMIASE ET MALADIE DE CHAGAS)

Chronic Chagas cardiomyopathy: characterization of cases and possibilities of action in primary healthcare.

Peres, T., Oliveira, S., Gomes, D., Prado, I., Lima, G., Soares, L., Limongi, J.
08-06-2022
Cad Saude Publica
https://pubmed.ncbi.nlm.nih.gov/35703667

Despite the drastic decrease in the incidence of Chagas disease in Brazil, past cases still greatly impact health services in the country. Thus, this study aimed to characterize Chagas disease cases regarding their cardiac staging and death prognosis and, based on that, to propose primary healthcare (PHC) case follow-ups. This is a cross-sectional study based on secondary data from the medical records of patients with chronic Chagas cardiomyopathy (CCC). A logistic regression was applied to estimate crude and adjusted odds ratios (OR). A total of 433 medical records were evaluated. More severe CCC cases were associated with a greater number of hospitalizations (OR = 3.41; 95%CI: 1.59-7.30) and longer hospitalization (OR = 3.15; 95%CI: 1.79-5.53). Cases with a higher risk of death were associated with a higher number of hospitalizations (OR = 1.92; 95%CI: 1.09-3.37), longer hospital stays (OR = 2.04; 95%CI: 1.30-3.18), and visits to the outpatient clinic (OR = 2.18; 95%CI: 1.39-3.41) and the emergency department of the assessed hospital (OR = 3.12; 95%CI: 1.27-7.66). Analyzing the medical records at two moments, 72.9% of the cases remained in the stages in which

they were initially evaluated. Overall, 44.4% of cases were classified as mild to moderate risk of death and 68.3% as low ones. The cases classified in the most severe stages of CCC and with high or intermediate risk of death were associated with greater hospital dependence. However, most cases were classified as milder forms of the disease, with a low risk of death and clinical stability. These findings aim to promote the role of PHC as a protagonist in the longitudinal follow-up of CCC cases in Brazil.

[Diagnostic protocol for febrile syndrome of respiratory origin in geographical areas of endemic risk of tropical infections].

Villamil-Gómez, W.
09-06-2022
Medicine (Madr)
https://doi.org/10.1016/j.med.2022.05.033

The syndromic surveillance of a group of diseases that have similar signs and symptoms, a common pathophysiology, and diverse etiology is aimed at rapidly detecting the presence of outbreaks which could potentially harm public health. This includes not only known outbreaks of infectious origin but also those of unknown origin. In patients suspected of having SARS-CoV-2/COVID-19, it is recommended to consider other etiologies of tropical fever in the differential diagnosis when these patients live in or come from endemic areas, as is the case of dengue, malaria, leptospirosis, acute Chagas disease, and rickettsiosis, among other endemic diseases. The possibility of SARS-CoV-2/AH1 AH5N1 MERS-CoV coinfection with these pathogens should also be considered.

Menthol carbonates as potent antiparasitic agents: synthesis and in vitro studies along with computer-aided approaches.

Clemente, C., Robledo, S., Ravetti, S.
13-06-2022
BMC Complement Med Ther
https://doi.org/10.1186/s12906-022-03636-8

Introduction: Despite the number of deaths and the significant economic and social costs associated with Chagas, Leishmaniasis and Malaria diseases worldwide, available drugs are limited and have serious side effects and high toxicity for the patient. Therefore, there is an urgent need for safe, low-cost, and effective treatments. Natural products are an important source of bioactive compounds and there is current interest in finding natural bioactive molecules that can be used for treating these parasitic diseases. In the present study we proposed to evaluate the in vitro antiparasitic activity of new menthol derivatives against Trypanosoma cruzi, Leishmania braziliensis and Plasmodium falciparum; moreover, we propose to explore their mode of action through in silico approaches. Material and methods: A series of carbonate prodrugs (1-9) were synthesized from menthol with different aliphatic alcohols. Spectroscopic techniques were used to confirm the structures of the synthesized compounds. The cytotoxicity of the compounds was assessed using U-937 cells. In vitro trypanocidal, leishmanicidal and antiplasmodial activity were evaluated using a T. cruzi, L. braziliensis and P. falciparum organism, respectively. In addition, in silico studies were also performed through molecular dynamics simulations and MM-PBSA analysis. Results: The assay revealed that most of the compounds were highly active against intracellular amastigotes of T. cruzi and L. braziliensis, and had moderate activity against the total forms of P. falciparum. Compound 2 was one of the drugs that showed a high selectivity index (SI) for the three organisms evaluated. The prediction of the ADME properties suggests that all the compounds have drug-like molecular properties and the probability to be lead candidates. Finally, molecular dynamics simulations, and MM-PBSA studies indicate that menthol at the substrate binding site of TcDHODH, LbDHODH and PfDHODH is structurally stable in the same order as the natural substrate; also, interactions of menthol with residues involved in the inhibition of TcDHODH and PfDHODH proteins were predicted. Conclusions: The present study demonstrates that menthol prodrugs are promising antiparasitic agents; however, the mechanisms of action proposed in this study need to be experimentally verified by future enzymatic assays.

Pan-Stage Real Time PCR for quantitation of Trypanosoma cruzi parasitic loads in blood samples.

Ramírez, J., Cao, L., Cruz-Saavedra, L., Hernandez, C., Castañeda, S., Muñoz, M., Ballesteros, N., Banu, R., Shrestha, P., Cordon-Cardo, C., Sordillo, E., Paniz-Mondolfi, A.
08-06-2022
Int J Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35690365

Chagas disease is a complex zoonosis caused by Trypanosoma cruzi, the diagnosis of this infection is complex and molecular tools are suggested to detect the parasite in blood samples. A long-standing question arises in Chagas disease molecular diagnostics and is related to the feasibility of using epimastigotes in standard curves to quantify parasitic loads. Herein, we conducted experiments running standard curves with all the known life stages of T. cruzi. Our results indicate that regardless the life stage employed, there are no statistically significant differences when calculating parasitic loads in blood samples. Our results have practical implications from a laboratory perspective in terms of the usability of epimastigotes to build standard curves for T. cruzi pan-stage assessment. Future studies are needed to further improve T. cruzi molecular diagnostic methods and enhance their impact in clinical practice.

Family cluster of Chagas disease among Bolivian immigrants in Italy: High rate of maternal-fetal transmission.

Antinori, S., Galimberti, L., Grande, R., Ricaboni, D., Sala, S., Giacomet, V., Colombo, V., Corbellino, M., Angheben, A., Giacomelli, A., Ridolfo, A.

08-06-2022
Travel Med Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35688417

Background: Chagas disease (CD) or American trypanosomiasis is a neglected anthropozoonosis caused by Trypanosoma cruzi that affects 6-8 million people worldwide (mainly in Latin America), 30-40% of whom develop cardiac or digestive complications. Once confined to endemic areas of Latin America, CD has more recently become a global disease as a result of migration flows from endemic to non-endemic regions, particularly in northern America and Europe. Congenital transmission is a particular challenge as it may be sustained for multiple generations and perpetuate the infection even in non-endemic countries. Methods: Subjects were identified during a cross-sectional survey of CD among Latin American people living in Milan, Italy. Serology was carried out using tests based on either a lysate and a recombinant antigen of Trypanosoma cruzi. They were also tested by a conventional Polymerase Chain Reaction (PCR) targeting the 330 bp variable region of the T. cruzi kinetoplast minicircle genome and a commercial real-time PCR. Results: We here describe a Bolivian family cluster with seven affected people with at least two autochthonous congenital T. cruzi infection which was identified during the course of a CD screening programme. We also review the epidemiology, diagnosis and control of congenital CD, with particular emphasis on the challenges facing the control and management of such a complex and still largely hidden disease. Conclusions: Our experience confirms the need to screen for CD all family members once a case is diagnosed and shows the possible high rate of congenital CD also in non-endemic areas.

Extracellular release of two peptidases dominates generation of the trypanosome quorum-sensing signal.

Tettey, M., Rojas, F., Matthews, K.
09-06-2022
Nat Commun
https://doi.org/10.1038/s41467-022-31057-1

Trypanosomes causing African sleeping sickness use quorum-sensing (QS) to generate transmission-competent stumpy forms in mammalian hosts. This density-dependent process is signalled by oligopeptides that stimulate the signal transduction pathway leading to stumpy formation. Here, using mass spectrometry analysis, we identify peptidases released by trypanosomes and, for 12 peptidases, confirm their extracellular delivery. Thereafter, we determine the contribution of each peptidase to QS signal production using systematic inducible overexpression in vivo, and confirm this activity operates through the physiological QS signalling pathway. Gene knockout of the QS-active peptidases identifies two enzymes, oligopeptidase B and metallocarboxypeptidase 1, that significantly reduce QS when ablated individually. Further, combinatorial gene knockout of both peptidases confirms their dominance in the generation of the QS signal, with peptidase release of oligopeptidase B mediated via an unconventional protein secretion pathway. This work identifies how the QS signal driving trypanosome virulence and transmission is generated in mammalian hosts.

African trypanosome strategies for conquering new hosts and territories: the end of monophyly?

Revue de littérature

Lukeš, J., Kachale, A., Votýpka, J., Butenko, A., Field, M.
06-06-2022
Trends Parasitol
https://pubmed.ncbi.nlm.nih.gov/35680542

Trypanosoma brucei parasites are the causative agents of African trypanosomiasis in humans, as well as surra, nagana, and dourine in animals. According to current widely used nomenclature, T. brucei is a group of five (sub)species, each causing a distinct disease and possessing unique genetic marker(s) or a combination thereof. However, minimal nuclear genome differences, sometimes accompanied by ongoing genetic exchange, robustly support polyphyly resulting from multiple independent origins of the (sub)species in nature. The ease of generating such (sub)species in the laboratory, as well as the case of overlapping hosts and disease symptoms, is incompatible with the current (sub)species paradigm, which implies a monophyletic origin. Here, we critically re-evaluate this concept, considering recent genome sequencing and experimental studies. We argue that ecotype should be used going forward as a significantly more accurate and appropriate designation.

Natural products from Annonaceae as potential antichagasic agents.

de Menezes, R., Tavares, J., Kato, M., da Rocha Coelho, F., Dos Santos, A., da Franca Rodrigues, K., Sessions, Z., Muratov, E., Scotti, L., Scotti, M.
08-06-2022
ChemMedChem
https://doi.org/10.1002/cmdc.202200196

Chagas disease, a neglected tropical disease, is endemic in 21 Latin American countries and particularly prevalent in Brazil. Chagas disease has drawn more attention in recent years due to its expansion into non-endemic areas. The aim of this work was to computationally identify and experimentally validate the natural products from an Annonaceae family as antichagasic agents. Through the ligand-based virtual screening, we identified 57 molecules with potential activity against the epimastigote form of T. cruzi . Then, 16 molecules were analyzed in the in vitro study, of which, six molecules displayed previously unknown antiepimastigote activity. We also evaluated these six molecules for trypanocidal activity. We observed that all six molecules have potential activity against the amastigote form, but no molecules were active against the trypomastigote form. 13-Epicupressic acid seems to be the most promising, as it was predicted as an active compound in the in silico study against the amastigote form of

T. cruzi , in addition to having in vitro activity against the epimastigote form.

Stroke in Chagas disease: from pathophysiology to clinical practice.

Lage, T., Tupinambás, J., Pádua, L., Ferreira, M., Ferreira, A., Teixeira, A., Nunes, M.
06-06-2022
Rev Soc Bras Med Trop
https://pubmed.ncbi.nlm.nih.gov/35674560

Despite substantial progress toward its control, Chagas disease continues to be a major public health problem in Latin America and has become a global health concern. The disease affects approximately 6 million people, of whom 20-40% will develop cardiomyopathy over the years after the initial Trypanosoma cruzi infection. Chagas cardiomyopathy is the most serious and frequent manifestation of Chagas disease. Clinical manifestations vary widely according to the severity of myocardial dysfunction, ranging from asymptomatic to severe forms, including dilated cardiomyopathy with heart failure, arrhythmias, thromboembolism events, and sudden death. Chagas disease is a risk factor for stroke regardless of the severity of cardiomyopathy, which is a leading cause of chronic disability. Classically, stroke etiology in patients with Chagas disease is thought to be cardioembolic and related to apical aneurysm, mural thrombus, and atrial arrhythmias. Although most strokes are thromboembolic, other etiologies have been observed. Small vessel disease, atherosclerosis, and cryptogenic diseases have been reported in patients with Chagas disease and stroke. The potential mechanisms involved in non-embolic strokes include the presence of associated risk factors, pro-inflammatory and prothrombotic disease states, and endothelial dysfunction. However, the contribution of each mechanism to stroke in Chagas disease remains unclear. The review aims to provide an overview of stroke in Chagas disease, highlighting the main pathophysiological mechanisms, clinical presentation, approaches for prevention, and unanswered questions regarding treatment strategies.

The challenge of risk assessment in the riddle of Chagas heart disease.

Marin-Neto, J., Rassi, A.
06-06-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35674530

Pathophysiology and new targets for therapeutic options in Chagas heart disease.

Ferreira, J.
06-06-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35674529

Prognosis of chronic Chagas heart disease and other pending clinical challenges.

Torres, R., Correia, D., Nunes, M., Dutra, W., Talvani, A., Sousa, A., Mendes, F., Scanavacca, M., Pisani, C., Moreira, M., de Souza, D., de Oliveira Junior, W., Martins, S., Dias, J.
06-06-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35674528

In this chapter, the main prognostic markers of Chagas heart disease are addressed, with an emphasis on the most recent findings and questions, establishing the basis for a broad discussion of recommendations and new approaches to managing Chagas cardiopathy. The main biological and genetic markers and the contribution of the electrocardiogram, echocardiogram and cardiac magnetic resonance are presented. We also discuss the most recent therapeutic proposals for heart failure, thromboembolism and arrhythmias, as well as current experience in heart transplantation in patients suffering from severe Chagas cardiomyopathy. The clinical and epidemiological challenges introduced by acute Chagas disease due to oral contamination are discussed. In addition, we highlight the importance of ageing and comorbidities in influencing the outcome of chronic Chagas heart disease. Finally, we discuss the importance of public policies, the vital role of funding agencies, universities, the scientific community and health professionals, and the application of new technologies in finding solutions for better management of Chagas heart disease.

Knockdown of E1- and E2-ubiquitin enzymes triggers defective chorion biogenesis and modulation of autophagy-related genes in the follicle cells of the vector Rhodnius prolixus.

Pereira, J., Dias, R., Ramos, I.
07-06-2022
J Cell Physiol
https://doi.org/10.1002/jcp.30806

In insects, the last stage of oogenesis is the process where the chorion layers (eggshell) are synthesized and deposited on the surface of the oocytes by the follicle cells. Protein homeostasis is determined by the fine-tuning of translation and degradation pathways, and the ubiquitin-proteasome system is one of the major degradative routes in eukaryotic cells. The conjugation of ubiquitin to targeted substrates is mediated by the ordered action of E1-activating, E2-conjugating, and E3-ligase enzymes, which covalently link ubiquitin to degradation-targeted proteins delivering them to the proteolytic complex proteasome. Here, we found that the mRNAs encoding polyubiquitin (pUbq), E1, and E2 enzymes are highly expressed in the ovaries of the insect vector of Chagas Disease Rhodnius prolixus. RNAi silencing of pUbq was lethal whereas the silencing of E1 and E2 enzymes resulted in drastic decreases in oviposition and embryo viability. Eggs produced by the E1- and E2-silenced insects presented particular phenotypes of altered chorion ultrastructure observed by high-resolution

scanning electron microscopy as well as readings for dityrosine cross-linking and X-ray elemental microanalysis, suggesting a disruption in the secretory routes responsible for the chorion biogenesis. In addition, the ovaries from silenced insects presented altered levels of autophagy-related genes as well as a tendency of upregulation in ER chaperones, indicating a disturbance in the general biosynthetic-secretory pathway. Altogether, we found that E1 and E2 enzymes are essential for chorion biogenesis and that their silencing triggers the modulation of autophagy genes suggesting a coordinated function of both pathways for the progression of choriogenesis.

Trypanosoma cruzi iron superoxide dismutases: insights from phylogenetics to chemotherapeutic target assessment.

Hickson, J., Athayde, L., Miranda, T., Junior, P., Dos Santos, A., da Cunha Galvão, L., da Câmara, A., Bartholomeu, D., de Souza, R., Murta, S., Nahum, L.
06-06-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05319-2

Background: Components of the antioxidant defense system in Trypanosoma cruzi are potential targets for new drug development. Superoxide dismutases (SODs) constitute key components of antioxidant defense systems, removing excess superoxide anions by converting them into oxygen and hydrogen peroxide. The main goal of the present study was to investigate the genes coding for iron superoxide dismutase (FeSOD) in T. cruzi strains from an evolutionary perspective. Methods: In this study, molecular biology methods and phylogenetic studies were combined with drug assays. The FeSOD-A and FeSOD-B genes of 35 T. cruzi strains, belonging to six discrete typing units (Tcl-TcVI), from different hosts and geographical regions were amplified by PCR and sequenced using the Sanger method. Evolutionary trees were reconstructed based on Bayesian inference and maximum likelihood methods. Drugs that potentially interacted with T. cruzi FeSODs were identified and tested against the parasites. Results: Our results suggest that T. cruzi FeSOD types are members of distinct families. Gene copies of FeSOD-A (n = 2), FeSOD-B (n = 4) and FeSOD-C (n = 4) were identified in the genome of the T. cruzi reference clone CL Brener. Phylogenetic inference supported the presence of two functional variants of each FeSOD type across the T. cruzi strains. Phylogenetic trees revealed a monophyletic group of FeSOD genes of T. cruzi TcIV strains in both distinct genes. Altogether, our results support the hypothesis that gene duplication followed by divergence shaped the evolution of T. cruzi FeSODs. Two drugs, mangafodipir and polaprezinc, that potentially interact with T. cruzi FeSODs were identified and tested in vitro against amastigotes and trypomastigotes: mangafodipir had a low trypanocidal effect and polaprezinc was inactive. Conclusions: Our study contributes to a better understanding of the molecular biodiversity of T. cruzi FeSODs. Herein we provide a successful approach to the study of gene/protein families as potential drug targets.

An Updated View of the *Trypanosoma cruzi* Life Cycle: Intervention Points for an Effective Treatment.

Revue de littérature

Martín-Escolano, J., Marín, C., Rosales, M., Tsaousis, A., Medina-Carmona, E., Martín-Escolano, R.
02-06-2022
ACS Infect Dis
https://doi.org/10.1021/acsinfecdis.2c00123

Chagas disease (CD) is a parasitic, systemic, chronic, and often fatal illness caused by infection with the protozoan *Trypanosoma cruzi*. The World Health Organization classifies CD as the most prevalent of poverty-promoting neglected tropical diseases, the most important parasitic one, and the third most infectious disease in Latin America. Currently, CD is a global public health issue that affects 6-8 million people. However, the current approved treatments are limited to two nitroheterocyclic drugs developed more than 50 years ago. Many efforts have been made in recent decades to find new therapies, but our limited understanding of the infection process, pathology development, and long-term nature of this disease has made it impossible to develop new drugs, effective treatment, or vaccines. This Review aims to provide a comprehensive update on our understanding of the current life cycle, new morphological forms, and genetic diversity of *T. cruzi*, as well as identify intervention points in the life cycle where new drugs and treatments could achieve a parasitic cure.

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.
07-06-2022
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.

LEISHMANIOSE

Analysis of Pharmacological Activities and Mechanisms of Essential Oil in Leaves of C. grandis 'Tomentosa' by GC-MS/MS and Network Pharmacology.

You, J., He, S., Chen, L., Guo, Z., Gao, F., Zhang, M., Dan, L., Chen, W.
10-06-2022
Comb Chem High Throughput Screen

https://doi.org/10.2174/1386207325666220610182644

Background: Citrus grandis 'Tomentosa', as the fruit epicarp of C. grandis 'Tomentosa' or C. grandis (L.) Osbeck, is widely used in health food and medicine. Actually, based on our survey results, there are also rich essential oils with bioativities in leaves, but the chemical compounds in this part and relevant pharmacological activities have never been studied systematically yet. Therefore, this study was to preliminarily decipher the pharmacological activities and mechanisms of the essential oil in leaves of C. grandis 'Tomentosa' by an integrated network pharmacology approach. **Methods:** Essential oil compositions from leaves of C. grandis 'Tomentosa' were identified using GC-MS/MS. And then the targets of these oil compositions were predicted and screened from TCMSP, SwissTargetPrediction, STITCH and SEA databases. STRING database was used to construct the protein-protein interaction networks, and the eligible protein targets were input into WebGestalt 2019 to carry out GO enrichment and KEGG pathway enrichment analysis. Based on the potential targets, disease enrichment information was obtained by TTD databases. Cytoscape software was used to construct the component-target-disease network diagrams. **Results:** Finally, 61 essential oil chemical components were identified by GC-MS/MS, which correspond to 679 potential targets. Biological function analysis showed that there were 12, 19, and 12 GO entries related to biological processes, cell components and molecular functions, respectively. 43 KEGG pathways were identified, of which the most significant categories were terpenoid backbone biosynthesis, TNF signaling pathway and leishmaniasis. The component-target-disease network diagram revealed that the essential oil compositions in leaves of C. grandis 'Tomentosa' could treat tumors, immune diseases, neurodegenerative diseases and respiratory diseases, which were highly related to CHRM1, PTGS2, CASP3, MAP2K1 and CDC25B. **Conclusion:** This study may provide a new insight into C. grandis 'Tomentosa' or C. grandis (L.) Osbeck and may provide useful information for future utilization and development.

Leishmania exposure in dogs from two endemic countries from New and Old Worlds (Brazil and Portugal): evaluation of three serological tests using Bayesian Latent Class Models.

Maia, C., Fraga, D., Cristóvão, J., Borja, L., da Silva Solcà, M., Campino, L., Veras, P., Gonçalves, L.

13-06-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05328-1

Background: Zoonotic leishmaniosis caused by Leishmania infantum is endemic in several countries of the Mediterranean Basin, Latin America, and Asia. Dogs are the main hosts and reservoirs of human infection. Thus, from a One Health perspective, early diagnosis of Leishmania infection in dogs is essential to control the dissemination of the parasite among other dogs and to humans. The aim of this study was to estimate the diagnosis accuracy of three serological tests to detect antibodies to Leishmania in dogs from two endemic settings using Bayesian latent class models (BLCM). **Methods:** A total of 378 dogs from two Portuguese and Brazilian endemic areas of leishmaniosis (194 animals from Portugal and 184 from Brazil) were screened. Detection of anti-Leishmania antibodies was performed using two commercial ELISA (L. infantum IgG-ELISA® and EIE-LVC®) and a rapid immunochromatographic test (DPP-LVC®). Bayesian latent class models were used to estimate Leishmania infection prevalence, together with sensitivities and specificities of the three diagnostic tests, in the two dog populations simultaneously. Predictive values were also calculated. Credibility intervals (CI) were obtained, considering different types of prior information. **Results** A posterior median Leishmania seroprevalence of 13.4% (95% CI 9.0-18.7) and of 21.6% (15.0-28.3) was estimated to the Portuguese and Brazilian dog subpopulations, respectively. The Bayesian analysis indicated that all tests were highly specific (specificity above 90%), and that the DPP-LVC® was more sensitive (96.6%; 83.1-99.9) than both ELISAs in the Portuguese subpopulation, while in the Brazilian subpopulation, EIE-LVC® and L. infantum IgG-ELISA®, had the highest sensitivity (88.2%; 73.7-97.0) and specificity (98.7%; 95.1-99.9), respectively. **Conclusions:** In general, the levels of diagnosis accuracy of the three serological tests to detect Leishmania antibodies assessed by BLCM indicate their utility in canine epidemiological studies. The same approach should be used to assess the performance of these techniques in the clinical management of infected and sick dogs using representative samples from the wide spectrum of clinical situations, namely from subclinical infection to manifest disease. The low positive predictive value of the serological tests used in the current protocol of the Brazilian Ministry of Health suggests that they should not be used individually and may not be sufficient to target reservoir-based control interventions.

Estimating the global demand curve for a leishmaniasis vaccine: A generalisable approach based on global burden of disease estimates.

Mohan, S., Revill, P., Malvolti, S., Malhame, M., Sculpher, M., Kaye, P.

13-06-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010471

Background: A pressing need exists to develop vaccines for neglected diseases, including leishmaniasis. However, the development of new vaccines is dependent on their value to two key players-vaccine developers and manufacturers who need to have confidence in the global demand in order to commit to research and production; and governments (or other international funders) who need to signal demand based on the potential public health benefits of the vaccine in their local context, as well as its affordability. A detailed global epidemiological analysis is rarely available before a vaccine enters a market due to lack of resources as well as insufficient global data necessary for such an analysis. Our study seeks to bridge this information gap by providing a generalisable

approach to estimating the commercial and public health value of a vaccine in development relying primarily on publicly available Global Burden of Disease (GBD) data. This simplified approach is easily replicable and can be used to guide discussions and investments into vaccines and other health technologies where evidence constraints exist. The approach is demonstrated through the estimation of the demand curve for a future leishmaniasis vaccine. **Methodology/Principal findings:** We project the ability to pay over the period 2030-2040 for a vaccine preventing cutaneous and visceral leishmaniasis (CL / VL), using an illustrative set of countries which account for most of the global disease burden. First, based on previous work on vaccine demand projections in these countries and CL / VL GBD-reported incidence rates, we project the potential long-term impact of the vaccine on disability-adjusted life years (DALYs) averted as a result of reduced incidence. Then, we apply an economic framework to our estimates to determine vaccine affordability based on the abilities to pay of governments and global funders, leading to estimates of the demand and market size. Based on our estimates, the maximum ability-to-pay of a leishmaniasis vaccine (per course, including delivery costs), given the current estimates of incidence and population at risk, is higher than $5 for 25-30% of the countries considered, with the average value-based maximum price, weighted by quantity demanded, being $5.7-6 [$0.3 - $34.5], and total demand of over 560 million courses. **Conclusion/Significance:** Our results demonstrate that both the quantity of vaccines estimated to be required by the countries considered as well as their ability-to-pay could make a vaccine for leishmaniasis commercially attractive to potential manufacturers. The methodology used can be equally applied to other technology developments targeting health in developing countries.

Reconstitution of Mycobacterium marinum Nonhomologous DNA End Joining Pathway in *Leishmania*.

Zhang, W., Wright, D., Harrison, L., Matlashewski, G.
13-06-2022
mSphere
https://doi.org/10.1128/msphere.00156-22

In mammalian cells, DNA double-strand breaks (DSBs) are mainly repaired by nonhomologous end joining (NHEJ) pathway. Ku (a heterodimer formed by Ku70 and Ku80 proteins) and DNA ligase IV are the core NHEJ factors. Ku could also be involved in other cellular processes, including telomere length regulation, DNA replication, transcription, and translation control. *Leishmania*, an early branching eukaryote and the causative agent of leishmaniasis, has no functional NHEJ pathway due to its lack of DNA ligase IV and other NHEJ factors but retains Ku70 and Ku80 proteins. In this study, we generated Leishmania donovani Ku70 disruption mutants and Ku70 and Ku80 double gene (Ku70/80) disruption mutants. We found that *Leishmania* Ku is still involved in DSB repair, possibly through its binding to DNA ends to block and slowdown 5' end resections and Ku-Ku or other protein interactions. Depending on location of a DSB between the direct repeat genomic sequences, *Leishmania* Ku could have an inhibiting effect, no effect or a promoting effect on the DSB repair mediated by single strand annealing (SSA), the most frequently used DSB repair pathway in *Leishmania*. Ku70/80 proteins are also required for the healthy proliferation of *Leishmania* cells. Interestingly, unlike in Trypanosoma brucei and L. mexicana, Ku70/80 proteins are dispensable for maintaining the normal lengths of telomeres in L. donovani. We also show it is possible to reconstitute the two components (Ku and Ligase D) NHEJ pathway derived from Mycobacterium marinum in *Leishmania*. This improved DSB repair fidelity and efficiency in *Leishmania* and sets up an example that the bacterial NHEJ pathway can be successfully reconstructed in an NHEJ-deficient eukaryotic parasite. **IMPORTANCE** Nonhomologous end joining (NHEJ) is the most efficient double-stranded DNA break (DSB) repair pathway in mammalian cells. In contrast, the protozoan parasite *Leishmania* has no functional NHEJ pathway but retains the core NHEJ factors of Ku70 and Ku80 proteins. In this study, we found that *Leishmania* Ku heterodimers are still participating in DSB repair possibly through blocking 5' end resections and Ku-Ku protein interactions. Depending on the DSB location, Ku could have an inhibiting or promoting effect on DSB repair mediated by the single-strand annealing repair pathway. Ku is also required for the normal growth of the parasite but surprisingly dispensable for maintaining the telomere lengths. Further, we show it is possible to introduce Mycobacterium marinum NHEJ pathway into *Leishmania*. Understanding DSB repair mechanisms of *Leishmania* may improve the CRISPR gene targeting specificity and efficiency and help identify new drug targets for this important human parasite.

tREPs-A New Class of Functional tRNA-Encoded Peptides.

Chakrabarti, A., Kaushik, M., Khan, J., Soota, D., Ponnusamy, K., Saini, S., Manvati, S., Singhal, J., Ranganathan, A., Pati, S., Dhar, P., Singh, S.
25-05-2022
ACS Omega
https://doi.org/10.1021/acsomega.2c00661

We asked if transfer RNA (tRNA) ever got an opportunity of translating its own sequence during evolution, what would have been the function of such tRNA-encoded peptides (tREPs)? If not, could one artificially synthesize tREPs to study the corresponding functional outcomes? Here, we report a novel, first-in-the-class, chemically synthesized tREP-18 molecule originating from the *Escherichia coli* tRNA sequence showing potent antileishmanial property. As a first step, *E. coli* tRNAs were computationally translated into peptide sequence equivalents and a database of full-length hypothetical tREPs was created. The tREP sequences were sent into sequence, structure, and energy filters to narrow down potential peptides for experimental validation. Based on the functional predictions, tREPs were screened against antiparasitic targets, leading to the identification of tREP-18 as a potential antiparasitic peptide. The in vitro assay of chemically synthesized tREP-18 on the *Ag83* strain of *Leishmania*

donovani showed its potent antileishmanial property (IC50 value of 22.13 nM). The atomic force microscopy and scanning electron microscopy images indicated significant alteration in the cytoskeletal architecture of tREP-18-treated parasites. Also, tREP-18 seems to destabilize the mitochondrial membrane potential of parasites, disrupting their cellular integrity and leading to parasitic death. The cellular assays of the tREP-18 peptide on the BS12 strain, a clinical isolate of post-kala azar dermal leishmaniasis, demonstrated its significant efficacy at an IC50 value of 15 nM. The tREP-18 peptide showed a toxic effect on the amastigote stage of the parasite, showing macrophage pathogen clearance at a concentration of 22.5 nM. This study provides the proof of the concept of making a new class of functional peptides from tRNA sequences. It also opens a huge untapped tRNA-peptide space toward novel discoveries and applications. In the future, it would be interesting to perform tREP edits and redesign tREPs toward specific applications.

"Models for cytotoxicity screenings of antileishmanial drugs: what has been done so far?"

Revue de littérature

Brioschi, M., Coser, E., Coelho, A., Gadelha, F., Miguel, D.
09-06-2022
Int J Antimicrob Agents
https://pubmed.ncbi.nlm.nih.gov/35691601

A growing number of studies have demonstrated the in vitro potential of an impressive number of antileishmanial candidates in the past years. However, the lack of uniformity regarding the choice of cell types for cytotoxicity assays may lead to uncomparable and inconclusive data. In vitro assays relying solely on non-phagocytic cell models may not represent a realistic result, as the effect of antileishmanials should be ideally presented based on its cytotoxicity profile against reticuloendothelial system cells. In the present review, we have assembled studies published in the scientific literature from 2015 to 2021 that explored leishmanicidal candidates, emphasizing the main host cell models used for cytotoxicity assays. The pros and cons of different host cell types and primary and cell lines are discussed to draw attention to the need of establishing standardized protocols for preclinical testing when assessing new antileishmanial candidates.

Auricular leishmaniasis in a child successfully treated with intralesional amphotericin B.

Diociaiuti, A., Giancristoforo, S., Calò Carducci, F., Bracaglia, C., Boni, A., Pane, S., Onetti Muda, A., De Benedetti, F., Putignani, L., El Hachem, M.
11-06-2022
Pediatr Dermatol
https://doi.org/10.1111/pde.15046

Cutaneous leishmaniasis (CL) is the most frequent form of leishmaniasis. The auricle is an extremely rare site for CL in the Old World. Auricular CL may be mistaken for other entities, such as relapsing polychondritis (RP). Here we report a pediatric case of Old World auricular CL mimicking RP in a child successfully treated with intralesional liposomal amphotericin B.

A mixed-methods approach to understanding domestic dog health and disease transmission risk in an indigenous reserve in Guyana, South America.

Milstein, M., Shaffer, C., Suse, P., Marawanaru, A., Heinrich, D., Larsen, P., Wolf, T.
10-06-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010469

Domestic dogs (Canis lupus familiaris) can transmit a variety of pathogens due to their ubiquitousness in urban, rural and natural environments, and their close interactions with wildlife and humans. In this study, we used a mixed-methods approach to assess the role of domestic dogs as potential intermediaries of disease transmission from wildlife to humans among indigenous Waiwai in the Konashen Community Owned Conservation Area, Guyana. To address these objectives we 1) performed physical examinations and collected biological samples to assess Waiwai domestic dog health, and 2) administered questionnaires to characterize the role of dogs in the community and identify potential transmission pathways between wildlife, dogs, and humans. We observed ectoparasites on all dogs (n = 20), including: fleas (100%), ticks (15%), botflies (30%), and jigger flea lesions (Tunga penetrans) (80%). Ten percent of dogs were seropositive for Ehrlichia canis/ewingii, 10% were positive for Dirofilaria immitis, and one dog was seropositive for Leishmania infantum. All dogs (n = 20) were seronegative for: canine distemper virus, Brucella canis, Leptospira serovars, Trypanosoma cruzi, Anaplasma phagocytophilum/platys and Borrelia burgdorferi. Our questionnaire data revealed that the Waiwai remove ectoparasites from their dogs, clean up dog feces, and administer traditional and/or Western medicine to their dogs. White blood cell, strongyle-type ova, and eosinophil counts were lower in dogs that were not frequently used for hunting, dogs that did receive traditional and/or western medicine, and dogs that were frequently kept in elevated dog houses, although differences were not statistically significant. While our results suggest that the Waiwai have developed cultural practices that may promote dog health and/or prevent zoonotic disease transmission, more research is necessary to determine the efficacy of these practices. Our study provides important data on the health of dogs and the potential for disease transmission to humans in a zoonotic hotspot.

Use of soil moisture active passive satellite data and WorldClim 2.0 data to predict the potential distribution of visceral leishmaniasis and its vector *Lutzomyia longipalpis* in Sao Paulo and Bahia states, Brazil.

Rodgers, M., Fonseca, E., Nieto, P., Malone, J., Luvall, J.,

McCarroll, J., Avery, R., Bavia, M., Guimaraes, R., Wen, X., Silva, M., Carneiro, D., Cardim, L.
08-06-2022
Geospat Health
https://doi.org/10.4081/gh.2022.1095

Visceral leishmaniasis (VL) is a neglected tropical disease transmitted by Lutzomyia longipalpis, a sand fly widely distributed in Brazil. Despite efforts to strengthen national control programs reduction in incidence and geographical distribution of VL in Brazil has not yet been successful; VL is in fact expanding its range in newly urbanized areas. Ecological niche models (ENM) for use in surveillance and response systems may enable more effective operational VL control by mapping risk areas and elucidation of eco-epidemiologic risk factors. ENMs for VL and Lu. longipalpis were generated using monthly WorldClim 2.0 data (30-year climate normal, 1-km spatial resolution) and monthly soil moisture active passive (SMAP) satellite L4 soil moisture data. SMAP L4 Global 3-hourly 9-km EASE-Grid Surface and Root Zone Soil Moisture Geophysical Data V004 were obtained for the first image of day 1 and day 15 (0:00-3:00 hour) of each month. ENM were developed using MaxEnt software to generate risk maps based on an algorithm for maximum entropy. The jack-knife procedure was used to identify the contribution of each variable to model performance. The three most meaningful components were used to generate ENM distribution maps by ArcGIS 10.6. Similar patterns of VL and vector distribution were observed using SMAP as compared to WorldClim 2.0 models based on temperature and precipitation data or water budget. Results indicate that direct Earth-observing satellite measurement of soil moisture by SMAP can be used in lieu of models calculated from classical temperature and precipitation climate station data to assess VL risk.

A family cluster of cutaneous Leishmania major infection unresponsive to intralesional meglumine antimonial: Case reports.

Ziaee, M., Ghatee, M., Taylor, W., Karamian, M.
06-06-2022
Indian J Med Microbiol
https://pubmed.ncbi.nlm.nih.gov/35680474

We describe a family cluster of L. major that became infected by traveling to an endemic focus of CL, which did not respond to intralesional meglumine antimonial treatment whilst two were hospitalized due to the progressive disease that responded to 4 weeks of oral ketoconazole. Parasite genotyping of the internal transcribed spacer 1 gene revealed the same infecting parasite strain in all family members and was the same strain in GenBank that caused mucosal L. major in a tourist who visited several North African countries. We hypothesise a reduced host immune response in the two hospitalized patients.

Downregulation of gamma subunit of TCP1 chaperonin of Leishmania donovani modulates extracellular vesicles-mediated macrophage microbicidal function.

Yadav, S., Anand, A., Chandra Balodi, D., Ramalingam, K., Mitra, K., Maras, J., Goyal, N.
06-06-2022
Microb Pathog
https://pubmed.ncbi.nlm.nih.gov/35680007

T-complex protein-1 (TCP1) is a group II chaperonin, known to fold various proteins like actin and tubulin. In Leishmania donovani only one subunit that is gamma subunit (LdTCP1γ) has been functionally characterized as a homo-oligomeric complex that exhibits ATP-dependent protein folding. The gene is essential for the survival and infectivity of the parasite. Leishmania parasite releases extracellular vesicles (EVs) containing numerous virulence factors, which play an essential role in parasite pathogenesis and modulate host immune cell signaling. The present study demonstrates that LdTCP1γ is secreted in the EVs and modulates host macrophage functions. EVs isolated from LdTCP1γ single-allele-replacement mutants significantly upregulate the microbicidal function of LPS-induced macrophage as evident by increased levels of proinflammatory cytokines (TNF-α, IL-6), iNOS and NO production. Further, the comparative proteomics of wild-type and single-allele-replacement mutant EVs showed that out of 876 identified proteins, 207 were significantly modulated. Among them, the top 50 modulated and abundantly secreted proteins constitute ~40% of the total identified protein intensity and include virulence factors such as GP63, peroxiredoxin, enolase, HSP70, elongation factor 2, amastin, eukaryotic translation initiation factor and α-tubulin. The comparative proteomic analysis revealed that the proteome enrichment of the EVs from LdTCP1γ single-allele replacement mutants significantly differs from wild-type EVs, which may be responsible for the altered host microbicidal responses. Thus, our data provide new insight into the role of LdTCP1γ in EVs-mediated host-parasite interactions.

Use of the intradermal leishmanin test (Montenegro skin test) for feline visceral leishmaniosis: Detection of cellular immunity.

Alves, M., Silva, D., Spada, J., Leonel, J., Benassi, J., Pereira, N., Vioti, G., Alves-Martin, M., Paula, N., Starke-Buzetti, W., Oliveira, T.
06-06-2022
Exp Parasitol
https://pubmed.ncbi.nlm.nih.gov/35679968

This study evaluated the humoral and cellular response in 100 cats living in an endemic area of visceral leishmaniosis (VL) using the Montenegro Skin Test (MST) and serological diagnosis and compared the MST with other diagnostic techniques. Sixty 60%, (60/100) cats were positive for MST and the diameter of positive skin reactions ranged from 5 to 9 mm. By serological methods, 74% (74/100) and 34% (34/100) had antibodies against Leishmania spp. by

Immunofluorescence Antibody Test (IFAT) and Indirect Enzyme-Linked Immunosorbent Assay (ELISA), respectively. Comparing tests, the observed profiles were (1) IFAT (+)/MST (-) = 27 cats, (2) IFAT(-)/MST(+) = 13 cats, (3) IFAT(+)/MST(+) = 47 cats, (4) ELISA(+)/MST(-) = 12 cats, (5) ELISA(-)/MST(+) = 38 cats and (6) ELISA(+)/MST(+) = 22 cats. Through the combination of serological diagnosis and MST, a positivity frequency of 87% (87/100) by IFAT + MST and 72% (72/100) by ELISA + MST was identified in this cat population. Five cats (5%) were positive for Leishmania donovani complex DNA by molecular analysis, and two cats (2%) had Leishmania spp. amastigotes in lymph node smears. Therefore, the agreement between tests was classified as poor for all tests by Kappa index. The IFAT (+)/MST (+) response was the most frequent considering all cats (47%; 47/100); nonetheless, the most frequent immune expression in Polymerase Chain Reaction (PCR)-positive cats was the IFAT (+)/MST (-) profile (80%; 4/5). Five sick and PCR-positive cats, negative for Feline Immunodeficiency Virus (FIV) and Feline Leukemia Virus (FeLV), that PCR sequencing matched 100% with L. donovani complex, all but one were MST negative. These results suggest that cats develop a significant cellular response against infection by parasites of the L. donovani complex, and most PCR and parasitological positive cats may be unable to develop a significant cellular response.

Spatiotemporal analysis of cutaneous leishmaniasis in Palestine and foresight study by projections modelling until 2060 based on climate change prediction.

Amro, A., Moskalenko, O., Hamarsheh, O., Frohme, M.
09-06-2022
PLoS One
https://doi.org/10.1371/journal.pone.0268264

Background: Cutaneous leishmaniasis (CL) is a vector-borne parasitic diseases of public health importance that is prevalent in the West Bank but not in the Gaza Strip. The disease caused by parasitic protozoans from the genus Leishmania and it is transmitted by infected phlebotomine sand flies. The aim of our study is to investigate the eco-epidemiological parameters and spatiotemporal projections of CL in Palestine over a 30-years period from 1990 through 2020 and to explore future projections until 2060. Methodology/Principal findings: This long-term descriptive epidemiological study includes investigation of demographic characteristics of reported patients by the Palestinian Ministry of Health (PMoH). Moreover, we explored spatiotemporal distribution of CL including future projection based on climate change scenarios. The number of CL patients reported during this period was 5855 cases, and the average annual incidence rate (AAIR) was 18.5 cases/105 population. The male to female ratio was 1.25:1. Patients-age ranged from 2 months to 89 years (mean = 22.5, std 18.67, and the median was 18 years). More than 65% of the cases came from three governates in the West Bank; Jenin 29% (1617 cases), Jericho 25% (1403), and Tubas 12% (658) with no cases reported in the Gaza Strip. Seasonal occurrence of CL starts to increase in December and peaked during March and April of the following year. Current distribution of CL indicate that Jericho, Tubas, Jenin and Nablus have the most suitable climatic settings for the sandfly vectors. Future projections until 2060 suggest an increasing incidence from northwest of Jenin down to the southwest of Ramallah, disappearance of the foci in Jericho and Tubas throughout the Jordan Vally, and possible emergence of new foci in Gaza Strip. Conclusions/Significance: The future projection of CL in Palestine until 2060 show a tendency of increasing incidence in the north western parts of the West Bank, disappearance from Jericho and Tubas throughout the Jordan Vally, and emergence of new CL endemic foci in the Gaza Strip. These results should be considered to implement effective control and surveillance systems to counteract spatial expansion of CL vectors.

Prevalence of Leishmania RNA virus in Leishmania parasites in patients with tegumentary leishmaniasis: A systematic review and meta-analysis.

Shita, E., Semegn, E., Wubetu, G., Abitew, A., Andualem, B., Alemneh, M.
08-06-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010427

Background: Cutaneous leishmaniasis is caused by different protozoan parasites of the genus Leishmania. Leishmania RNA virus (LRV) was identified as the first Leishmania infecting virus in 1998. Different studies showed the presence and role of the LRV in Leishmania parasites causing cutaneous leishmaniasis (CL). However, there is limited data on the pooled prevalence of LRV in Leishmania parasites causing CL. Therefore, the aim of this systematic review and meta-analysis was to determine the pooled prevalence of LRV in Leishmania parasite isolates and/or lesion biopsies in patients with CL from the available literature globally. Methodology: We retrieved the studies from different electronic databases. The studies were screened and identified based on the inclusion and exclusion criteria. We excluded studies exclusively done in experimental animals and in vitro studies. The review was conducted in line with PRISMA guidelines. The meta-analysis was performed with Stata software version 14 with metan command. The forest plot with random-effect model was used to estimate the pooled prevalence with 95% confidence interval. Inverse variance index (I2) was used to assess the heterogeneity among the included articles. Principal findings: A total of 1215 samples from 25 studies were included. Of these, 40.1% (487/1215) were positive for LRV. The overall pooled prevalence of LRV globally was 37.22% (95% CI: 27.54% - 46.90%). The pooled prevalence of LRV in the New World (NW) and Old World (OW) regions was 34.18% and 45.77%, respectively. Leishmania guyanensis, L. braziliensis, L. major, and L. tropica were the most studied species for the detection of LRV. The prevalence of LRV from Leishmania isolates and lesion biopsies was 42.9% (349/813) and 34.3% (138/402), respectively. Conclusion: This systematic study revealed that there is high prevalence of LRV in Leishmania parasites

isolated from patients with CL. More comprehensive studies would be required to investigate the presence of the LRV in other Leishmania species such as L. aethiopica to fully understand the role of LRV in different clinical manifestations and disease pathology presented in CL patients.

Are the clinical features of leprosy and American tegumentary leishmaniasis worse in patients with both diseases?

Carvalho, A., Luz, J., Steinmann, P., Ignotti, E.
06-06-2022
Rev Inst Med Trop Sao Paulo
https://pubmed.ncbi.nlm.nih.gov/35674635

This cross-sectional population-based study compared clinical features of leprosy and American tegumentary leishmaniasis (ATL) in patients diagnosed with both diseases (n=414) and in those diagnosed with only leprosy (n=27,790) or only ATL (n=24,357) in Mato Grosso State, which is a hyperendemic area for both diseases in Midwest Brazil. All new cases of leprosy and ATL reported in the area from 2008 to 2017 were included. Patients diagnosed with both diseases were identified by a probabilistic linkage procedure applied to leprosy and ATL databases of the national reporting system. The distribution of the frequency of clinical features between groups was compared by the chi-square test, followed by a multivariate logistic regression. Patients diagnosed with both leprosy and ATL presented higher odds of having nerve damage (OR: 1.34; 95% CI: 1.09-1.66) and leprosy reactions (OR: 1.35; 95% CI: 1.04-1.76) compared to patients diagnosed only with leprosy. Mucocutaneous leishmaniasis (OR: 2.29; 95% CI: 1.74-3.00) was more frequent among patients with both diagnoses when compared to patients who only had ATL. In conclusion, patients diagnosed with both leprosy and ATL present more severe clinical features of such diseases. Our data can be useful for designing health policies aimed at timely and integrated management of leprosy and ATL in co-endemic areas.

Ageing impairs protective immunity and promotes susceptibility to murine visceral leishmaniasis.

Salgado, C., Corea, A., Covre, L., De Matos Guedes, H., Falqueto, A., Gomes, D.
07-06-2022
Parasitology
https://doi.org/10.1017/S0031182022000828

Fever in the Returning Traveler.

Paquet, D., Jung, L., Trawinski, H., Wendt, S., Lübbert, C.
07-06-2022
Dtsch Arztebl Int
https://doi.org/10.3238/arztebl.m2022.0182

Background: It is predicted that approximately two billion tourist trips to foreign countries will be taken worldwide each year by 2030. Germany has long been among the most active countries in tourism. The frequency of illness among persons returning from developing and newly industrialized countries is 43-79%. The appropriate diagnosis of fever in returning travelers is a clinically important matter, as it can be a sign of a life-threatening illness. Methods: This review is based on publications (2001-2022) retrieved by a selective search in PubMed for studies on the epidemiology, diagnosis, and treatment of febrile illnesses in returning travelers, or on specific tropical diseases. Results: Diarrhea, fever, and skin changes are the most common manifestations of disease after travel to tropical and subtropical areas. The diagnostic evaluation should be performed in a series of steps, beginning with a precise travel history and the identification of specific risk factors. Among travelers returning from sub-Saharan Africa, Plasmodium falciparum malaria is the most common cause of fever on presentation to centers for infectious diseases and tropical medicine, affecting approximately 50 per 1000 travelers. Among persons returning from travel to Southeast Asia, dengue fever is the most common infectious disease, affecting 50-160 per 1000 travelers. Further potentially dangerous diseases include chikungunya and zika fever, typhoid and paratyphoid fever, amoebic liver abscess, visceral leishmaniasis (kala-azar), leptospirosis, and, very rarely, imported cases of viral hemorrhagic fever. COVID-19 and influenza are important differential diagnoses. Conclusion: The differential diagnosis can be narrowed by thorough history-taking with particular attention to the patient's travel route, combined with a good knowledge of the geographic spread and incubation times of the main tropical diseases. Algorithms help clinicians to focus the diagnostic work-up and select the appropriate further laboratory tests and diagnostic procedures.

Improved efficacy of meglumine antimoniate incorporated in anionic liposomes against Leishmania infantum infecting canine macrophages.

Ortega, V., Radaic, A., de Jesus, M., de Paula, E., Giorgio, S.
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J Pharm Pharmacol
https://doi.org/10.1093/jpp/rgab081

Objectives: Leishmaniasis is a zoonotic disease and several drugs have been used in the treatment, including meglumine antimoniate (AME). The chemotherapy reaches clinical cure but does not eliminate parasites, contributing to drug resistance. To improve AME efficacy we incorporated it in anionic liposomes. The antiparasitic activity and intracellular localization were investigated in canine macrophages infected with Leishmania infantum. Methods: Liposomes (L-AME) is composed of egg phosphatidylcholine, cholesterol, palmitoyl oleoyl phosphatidyl serine and α-tocopherol (4 : 3 : 0.4 : 0.07 mol%) plus AME. L-AME size, polydispersity, zeta potential and morphology were analysed as well as antileishmanial activity and intracellular localization in DH82 macrophages. Key findings: Liposomes (360 nm) zeta potential range from -40 to -65 mV, had 23% encapsulation efficiency and were stable for 180 days at 4°C. Free AME was cytotoxic towards L. infantum

infected macrophages (ID50 = 0.012 M) while L-AME did not reduce cell viability. L-AME colocalized with parasites inside macrophages in a time-dependent manner, and reduced the percentage of infected cells and the number of intracellular parasites, decreasing the infection index (75-80%) twice as compared with AME treatment. **Conclusions:** Liposomal AME is a promising delivery system for treating visceral leishmaniasis, improving meglumine efficacy against L. infantum and minimizing its cytotoxicity towards canine macrophages.

CYSTICERCOSE

Knowledge, attitudes and practices related to Taenia solium cysticercosis and taeniasis in Tanzania.

Nyangi, C., Stelzle, D., Mkupasi, E., Ngowi, H., Churi, A., Schmidt, V., Mahonge, C., Winkler, A.
13-06-2022
BMC Infect Dis
https://doi.org/10.1186/s12879-022-07408-0

Background: Taenia solium cysticercosis/taeniasis (TSCT) is reported to be endemic in pig producing areas around the world, causing significant disease burden and economic losses. **Methods:** This cross-sectional study aimed at assessing Knowledge, Attitudes and Practices (KAP) regarding TSCT in four districts, namely Mbulu, Mpwapwa, Mbinga, and Rungwe in Tanzania. Data on KAP were collected through questionnaire-based interviews and household infrastructure observations. **Results:** Knowledge about porcine cysticercosis was good, particularly among pig keepers across the districts. Many participants had heard about the pork tapeworm (T. solium taeniasis), and the knowledge about signs/symptoms and treatment was fair, but the means of transmission and prevention measures were often unknown. Whilst most participants were familiar with epilepsy, no one knew anything about human cysticercosis and the link between cysticercosis and epileptic seizures. A similar trend is reflected through the attitudes toward the low risk perception of cysticercosis infection. Not surprisingly, the risk perception of the infection with the pork tapeworm was low too. Many participants reported not washing their hands before eating or after using the toilet which highlights potential risks for the development of human cysticercosis. Albeit nearly every participant reported using the toilet always, household observations revealed that toilets were either lacking or had no complete walls. Generally, household observations revealed a discrepancy between questionnaire answers on the one hand and the availability of toilet and handwashing facilities and the confinement of pigs on the other hand. **Conclusion:** This study demonstrates knowledge gaps and adverse practices which may hinder and/or slow down the control/elimination of T. solium in endemic countries. The study results are also useful for appropriate designing of TSCT health interventions that need to be planned carefully, taking into account the local context and designing TSCT in partnership with the local communities from the beginning to the end applying a One Health approach to allow the possible sustained and best impacts.

A chromosome-level genome assembly for the rabbit tapeworm Taenia pisiformis.

Pu, L., Liu, Z., Guo, A., Wu, B., Liu, G., Zhang, S., Guo, X., Li, X., Jian, J., Cai, X., Wang, S.
06-06-2022
Gene
https://pubmed.ncbi.nlm.nih.gov/35680022

Taenia pisiformis is one of the most widespread gastrointestinal parasites and its larvae (cysticercosis) causes significant economic loss to rabbit industry. No efficient drug is available for this disease to date. To better understand its genomics, we assembled a 211-Mb high quality genome of T. pisiformis at chromosome level with a scaffold N50 size of 20 Mbp. Totally, 12,097 protein-coding genes was predicted from the genome. Genome-level phylogenetic analysis confirmed the taxonomic affiliations with other tapeworms and revealed that T. pisiformis diverged from its closely related relative T. hydatigena ~14.6 Mya. Comparative genomic analyses revealed that the T. pisiformis genome was characterized by adaptive features of strong positive selection signals from carbohydrate/lipid metabolism and body surface integrity, and of expanded gene families related to metabolism of amino acids and lipids. The high-quality genome of T. pisiformis constitutes a resource for the comparative genomics and for further applications in general parasitology.

DRACUNCULOSE

ECHINOCOCCOSE

Global analysis of neuropeptides in cestodes identifies Attachin, a SIFamide homolog, as a stimulant of parasite motility and attachment.

Preza, M., Van Bael, S., Temmerman, L., Guarnaschelli, I., Castillo, E., Koziol, U.
11-06-2022
J Neurochem
https://doi.org/10.1111/jnc.15654

Many anthelmintics target the neuromuscular system, in particular by interfering with signalling mediated by classical neurotransmitters. Although peptidergic signalling has been proposed as a novel target for anthelmintics, current knowledge of the neuropeptide complement of many

helminth groups is still limited, especially for parasitic flatworms (cestodes, trematodes and monogeneans). In this work, we have characterised the neuropeptide complement of the model cestode Hymenolepis microstoma. Peptidomic characterization of adults of H. microstoma validated many of the neuropeptide precursor (npp) genes previously predicted in silico, and identified novel neuropeptides that are conserved in parasitic flatworms. Most neuropeptides from parasitic flatworms lack significant similarity to those from other animals, confirming the uniqueness of their peptidergic signalling. Analysis of gene expression of ten npp genes by in situ hybridization confirmed that all of them are expressed in the nervous system and identified cryptic features, including the first evidence of dorsoventral asymmetry, as well as a new population of peripheral peptidergic cells that appears to be conserved in the trematode Schistosoma mansoni. Finally, we characterised in greater detail Attachin, an SIFamide homolog. Although its expression is largely restricted to the longitudinal nerve cords and cerebral commissure in H. microstoma, it shows widespread localization in the larval nervous system of Echinococcus multilocularis and Mesocestoides corti. Exogenous addition of a peptide corresponding to the highly conserved C-terminus of Attachin stimulated motility and attachment of M. corti larvae. Altogether, this work provides a robust experimental foothold for the characterization of peptidergic signalling in parasitic flatworms.

Cystic echinococcosis in slaughtered sheep in Erzurum province, Turkey.

Avcioglu, H., Bia, M., Balkaya, I., Kirman, R., Akyuz, M., Guven, E.
07-06-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35688264

Cystic echinococcosis (CE) is an important zoonotic infection caused by the larval stages of the genus Echinococcus. Turkey is a highly endemic region for CE and the disease is one of the major public health problems. The study was aimed to assess the situation of the CE in sheep in Turkey and also to provide data on circulating genotypes in the country. A total of 3319 sheep at slaughter were screened during the study. The prevalence of CE in the study area was 31.7% (1052/3319). The lungs were the most frequently CE infected organ (52.6%, 526/1052). Microscopic examination revealed that overall cyst fertility was 68.1%. Molecular analysis of partial fragments of 12S and COI gene regions were included for 351 selected cyst samples and all of them were identified as E. granulosus sensu stricto. Sequence analysis showed that the predominant genotype in the study areas was G1 (77.1%), and the rest were G3 (22.9%). The prevalence rate of CE in sheep in the study area is lower compared to previous years except for one province. Considering the high cyst fertility rate and the predominance of E. granulosus G1 which is particularly pathogenic to humans, calls for serious control measures like public awareness about the disease, sufficient dog deworming programs, continuity of monitoring the disease should be taken.

Expanding the family of Mu-class glutathione transferases in the cestode parasite Echinococcus granulosus sensu lato.

Miles, S., Mourglia-Ettlin, G., Fernández, V.
06-06-2022
Gene
https://pubmed.ncbi.nlm.nih.gov/35680021

Glutathione transferases (GSTs) perform catalytic and non-catalytic activities, mostly involved in stress-response and cell detoxification. Helminth parasites express several GSTs of multiple classes that are involved in the neutralization of potentially harmful oxidants, and in the inactivation or removal of xenobiotics. Additionally, GSTs participate in immunomodulatory processes that facilitate the parasite establishment and survival within its host. In Echinococcus granulosus sensu lato (s.l.) -the cestode parasite responsible for cystic echinococcosis- only one Mu-class GST has been reported. In the present work, by using bioinformatic and proteomic approaches we searched for novel Mu-class GSTs potentially involved in the parasite oxidative-stress metabolism. In the genome of E. granulosus s.l., 6 GST-related sequences were found to constitute a strongly conserved phylogenetical clade with Mu-class members. Among them, 5 displayed conserved gene structure (exon/intron), as well as specific residues and motifs characteristic of Mu-class enzymes. By proteomic analysis, 3 Mu-GSTs were identified to be expressed in the protoscolex parasite stage, 2 of them being firstly described as Mu-class GSTs here. The existence of more than one productive Mu-GST gene expands the parasite xenobiotic phase II metabolism, which might have beneficial roles on E. granulosus s.l. ability to successfully infect its host.

Alveolar echinococcosis in a dog in Missouri, USA.

Kuroki, K., Morishima, Y., Dorr, L., Cook, C.
09-06-2022
J Vet Diagn Invest
https://doi.org/10.1177/10406387221104754

A 10-y-old, castrated male Boxer dog that was born and had lived in Missouri without any travel history to other states, except for a few trips to Kansas, was presented with a distended abdomen and declined health. Ultrasonographic examination revealed a large hepatic mass, and the dog was euthanized. A postmortem examination revealed that the left liver lobes were largely replaced by a white-to-tan multilobular mass with a cobblestone surface. The lesion also involved the diaphragm. Histologically, hepatic architecture was effaced by large areas of necrosis with numerous, ≤0.2-cm, cystic structures that stained positively with periodic acid-Schiff stain and contained calcareous corpuscles. Gross and microscopic hepatic lesions were compatible with alveolar echinococcosis (AE) caused by *Echinococcus multilocularis*. PCR examination confirmed *E. multilocularis*, and results from genotyping were consistent with the E4 haplotype. To our knowledge, this is only the second canine AE case and the third pet dog that has been confirmed to be infected by *E. multilocularis* in the contiguous United States. *E. multilocularis* is a serious health risk for both pet dogs and humans.

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

Passarelli, P., Ramchandar, N., Naheedy, J., Kling, K., Choi, L., Pong, A.
07-06-2022
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.

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

Efficacy of drugs against clonorchiasis and opisthorchiasis: a systematic review and network meta-analysis.

Qian, M., Patel, C., Palmeirim, M., Wang, X., Schindler, C., Utzinger, J., Zhou, X., Keiser, J.
10-06-2022
Lancet Microbe
https://pubmed.ncbi.nlm.nih.gov/35697047

Background: Clonorchis sinensis, Opisthorchis viverrini, and Opisthorchis felineus are the three most important human liver fluke species in the Opisthorchiidae family, infecting approximately 25 million people worldwide. Drug treatment is needed to control morbidity and is also useful in lowering transmission. Several drugs used in various regimens are available to treat these infections, but their comparative efficacy is uncertain. We aimed to compare the efficacy in terms of cure rate and egg reduction rate of currently registered drugs against human liver fluke infection. Methods: We conducted a systematic review using readily available electronic databases (MEDLINE, Embase, Cochrane Central Register of Controlled Trials, KoreaMed, China National Knowledge Infrastructure, and Wanfang Data) without language restrictions from inception until June 29, 2021. Clinical trials with pairwise comparison of drugs (praziquantel, albendazole, mebendazole, tribendimidine, or combinations of these drugs) against C sinensis, O viverrini, and O felineus were eligible, including trials comparing these drugs or their combinations with placebo. We compared efficacy in terms of cure rate by network meta-analysis. We conducted mixed binomial regression analyses for each species to derive predicted median cure rates for each drug regimen. The models included treatment and infection intensity as fixed factors, year of publication as covariate, and random effects of the different studies assumed to be normally distributed. We also assessed the quality of the included studies. This study was registered with PROSPERO (CRD42018109232). Findings: Overall, 26 trials from 25 studies were included, of which 18 involved C sinensis, seven studied O viverrini, and one focused on O felineus. These trials included a total of 3340 participants. The two long-term treatment courses against C sinensis infection using 400 mg of albendazole (400 mg twice a day for 5 days and 400 mg twice a day for 7 days) resulted in cure rates of 100%, while two other multiple-dose regimens of albendazole resulted in high predicted cure rates: 300 mg twice a day for 5 days (93·9% [95% CI 49·6-99·6]) and 400 mg twice a day for 3 days (91·0% [50·9-99·0]). The WHO-recommended praziquantel regimen (25 mg/kg three times a day for 2 days) also showed a high predicted cure rate (98·5% [85·4-99·9]) in C sinensis infection, and predicted cure rates were above 90% for several other multiple-dose praziquantel regimens, including 20 mg/kg three times a day for 3 days (97·6% [74·7-99·8]), 14 mg/kg three times a day for 5 days (93·9% [44·8-99·7]), and 20 mg/kg twice a day for 3 days (91·0% [50·9-99·0]). In O viverrini infection, the regimen of 50 mg/kg and 25 mg/kg of praziquantel given in a single day showed the highest predicted cure rate (93·8% [85·7-97·5]), while a single dose of 50 mg/kg praziquantel also resulted in a high predicted cure rate (92·1% [64·9-98·6]). The single dose of 400 mg tribendimidine showed a high predicted cure rate of 89·8% (77·5-95·8). A low quality of evidence was demonstrated in most studies, especially those published before 2000. Selection bias due to poor random sequence generation and allocation concealment was high, and performance and detection biases were frequently unreported. Interpretation: Praziquantel shows high efficacy against clonorchiasis and opisthorchiasis. Tribendimidine might serve as a treatment alternative and warrants further investigation. Although albendazole is efficacious when long treatment schedules (5 days or 7 days) are applied, limited size of studies and high risk of bias affect the interpretation of results. More high-quality studies are needed to promote the establishment of treatment guidelines for human liver fluke infection. Funding: Fourth Round of Three-Year Public Health Action Plan (2015-2017; Shanghai, China) and Swiss National Science Foundation.

FILARIOSE LYMPHATIQUE

Integrated transmission assessment surveys (iTAS) of lymphatic filariasis and onchocerciasis in Cross River, Taraba and Yobe States, Nigeria.

Anagbogu, I., Saka, Y., Surakat, O., Okoronkwo, C., Davies, E., Oyale, P., Ekpo, U., Amazigo, U., Barbre, K., Igbe, M., Nyior, A., Jacob, S., Gideon Nteun, U., Abubakar Umar, Z.
13-06-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05302-x

Background: Integrated transmission assessment surveys (iTAS) have been recommended for evaluation of the transmission of both lymphatic filariasis (LF) and onchocerciasis as the prevalence of both diseases moves toward their respective elimination targets in Nigeria. Therefore, we conducted an iTAS between May and December 2017 in five local government areas (LGAs), also known as implementation units (IUs), in states of Cross River, Taraba and Yobe in Nigeria. Methods: The TAS comprised two phases: the Pre-iTAS and the iTAS itself. Three states (Cross River, Taraba and Yobe), comprising five LGAs and 20 communities that have completed five rounds of combined treatment with ivermectin and albendazole for LF and 12 total rounds of ivermectin, were selected for inclusion in the study. All participants were tested with the Filariasis Test Strip (FTS; Alere Inc.) and the Biplex rapid Diagnostic Test (RDT; identifying filaria antigens Ov16/Wb123; Abbott diagnosctics Korea Inc.). Pre iTAS included 100 children ages 5-9 in each 4 communities and 300 individuals ages 10 and older in a subset of two communities. For the iTAS, only LGAs where antigenemia prevalence in all sampled communities during the Pre-iTAS was < 2% for LF were selected. Results: Of the five LGAs included in the study, four met the cutoff of the Pre-iTAS and were included in the iTAS; the Ikom LGA was excluded from the iTAS due to antigenemia prevalence. A total of 11,531 school-aged children from 148 schools were tested for LF and onchocerciasis across these four LGAs, including 2873 children in Bade, 2622 children in Bekwara, 3026 children in Gashaka and 3010 children in Karim Lamido. Using the FTS, all samples from Bade and Karim Lamido were negative, whereas 0.2% of the samples from Bekwara and Gashaka were positive. Using the Biplex RDT, LF prevalence in Bade, Bekwara, Gashaka and Karim Lamido was<0.1%, 0.5%, 0.4% and<0.1%, respectively. Moreover, all samples from Bade and Karim Lamido were negative for onchocerciasis, whereas 3.1% and 1.8% of the samples from Bekwara and Gashaka were positive, respectively. Conclusion: This study has provided additional information on the current burden of onchocerciasis and LF in the four IUs sampled where mass drug administration (MDA) for both infections has been ongoing for years. The study identifies that LF-MDA can be safely stopped in all four of the IUs studied, but that MDA for onchocerciasis needs to continue, even though this may pose a challenge for LF surveillance. Based on the preliminary results from all four sites, this study has fulfilled the primary objective of determining the programmatic feasibility of an iTAS as a tool to simultaneously assess onchocerciasis and LF prevalence in areas co-endemic for the two infections that have completed the recommended treatment for one or both infections, and to make decisions on how to proceed.

Human Filariasis in Travelers and Migrants: A Retrospective 25-year Analysis at the Institute of Tropical Medicine, Antwerp, Belgium.

Revue de littérature

Bottieau, E., Huits, R., Van Den Broucke, S., Maniewski, U., Declercq, S., Brosius, I., Theunissen, C., Feyens, A., Van Esbroeck, M., van Griensven, J., Clerinx, J., Soentjens, P.

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Clin Infect Dis

https://doi.org/10.1093/cid/ciab751

Background: Information on human filariasis in international travelers is scarce. We describe the epidemiology, clinical presentation, and outcome of these infections in a reference travel clinic over the past decades. Methods: We reviewed all cases of filariasis diagnosed at the Institute of Tropical Medicine, Antwerp, Belgium, from 1994 to 2018. Diagnosis was obtained by either parasitological methods (confirmed) or strict clinical case definitions (probable). We assessed the characteristics of cases at diagnosis and response to therapy within 3-12 months. Results: A total of 320 patients (median age: 41 years; 71% males) were diagnosed with 327 filarial infections (Wuchereria bancrofti = 6, Onchocerca volvulus = 33, Loa loa = 150, Mansonella perstans = 130, unspecified species = 8). Diagnosis was confirmed in 213/320 (67%) patients. European long-term travelers accounted for 166 patients (52%) and visitors/migrants from tropical countries for another 110 (34%). Central Africa was the likely region of acquisition for 294 (92%) patients. The number of filariasis cases decreased from 21.5/year on average in the 1990s to 6.3/year in the past decade, when loiasis became predominant. Cases reported symptoms in >80% of all filarial infections but mansonellosis (45/123 single infections; 37%). Lymphatic filariasis and onchocerciasis cases responded well to conventional therapy. However, 30% of patients with loiasis and mansonellosis experienced treatment failure (with diethylcarbamazine and levamisole-mebendazole, respectively). Conclusions: The burden and species distribution of filariasis in travelers evolved in the past decades. Most presentations were symptomatic. Case management would benefit from more effective therapies for loiasis and mansonellosis.

MYCETOME

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

Lim, W., Verbon, A., van de Sande, W.

09-06-2022

Expert Opin Drug Discov

https://doi.org/10.1080/17460441.2022.2080195

Introduction: The three fungal skin neglected tropical diseases (NTD) - mycetoma, chromoblastomycosis and sporotrichosis - currently lack prioritization and support to establish drug discovery programs in search for novel treatment options. This has made the efforts to identify novel drugs for these fragmented skinNTDs. Areas covered: To help escalate the discovery of novel drugs to treat these fungal skinNTDs, the

authors have prepared an overview of the compounds with activity against fungal skinNTDs by analyzing data from individual drug discovery studies, including those performed on the Medicines for Malaria Venture (MMV) open access boxes. Expert opinion: The authors were unable to identify studies in which causative agents of all three skinNTDs were included, indicating that an integrated approach is currently lacking. From current available data, the azoles and iodoquinol were the only compounds with activity against causative agents from the three different fungal skinNTDs. Fungal melanin inhibition enhanced the activity of antifungal agents. For mycetoma, the fenarimols, aminothiazoles and benzimidazole carbamates are currently being investigated in the MycetOS initiative. To come to a more integrated approach to identify drugs active against all three fungal skinNTDs, compounds made in the MycetOS initiative could also be explored for chromoblastomycosis and sporotrichosis.

ONCHOCERCOSE

Human Filariasis in Travelers and Migrants: A Retrospective 25-year Analysis at the Institute of Tropical Medicine, Antwerp, Belgium.

Revue de littérature

Bottieau, E., Huits, R., Van Den Broucke, S., Maniewski, U., Declercq, S., Brosius, I., Theunissen, C., Feyens, A., Van Esbroeck, M., van Griensven, J., Clerinx, J., Soentjens, P.

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Clin Infect Dis

https://doi.org/10.1093/cid/ciab751

Background: Information on human filariasis in international travelers is scarce. We describe the epidemiology, clinical presentation, and outcome of these infections in a reference travel clinic over the past decades. Methods: We reviewed all cases of filariasis diagnosed at the Institute of Tropical Medicine, Antwerp, Belgium, from 1994 to 2018. Diagnosis was obtained by either parasitological methods (confirmed) or strict clinical case definitions (probable). We assessed the characteristics of cases at diagnosis and response to therapy within 3-12 months. Results: A total of 320 patients (median age: 41 years; 71% males) were diagnosed with 327 filarial infections (Wuchereria bancrofti = 6, Onchocerca volvulus = 33, Loa loa = 150, Mansonella perstans = 130, unspecified species = 8). Diagnosis was confirmed in 213/320 (67%) patients. European long-term travelers accounted for 166 patients (52%) and visitors/migrants from tropical countries for another 110 (34%). Central Africa was the likely region of acquisition for 294 (92%) patients. The number of filariasis cases decreased from 21.5/year on average in the 1990s to 6.3/year in the past decade, when loiasis became predominant. Cases reported symptoms in >80% of all filarial infections but mansonellosis (45/123 single infections; 37%). Lymphatic filariasis and onchocerciasis cases responded well to conventional therapy. However, 30% of patients with loiasis and mansonellosis experienced treatment failure (with diethylcarbamazine and levamisole-mebendazole, respectively). Conclusions: The burden and species distribution of filariasis in travelers evolved in the past decades. Most presentations were symptomatic. Case management would benefit from more effective therapies for loiasis and mansonellosis.

SCHISTOSOMIASE

Adsorption of praziquantel enantiomers on chiral cellulose tris 3-chloro, 4-methylphenylcarbamate by frontal analysis: Fisherian and Bayesian parameter estimation and inference.

Cavalcante Dos Santos, R., Cunha, F., Marcellos, C., de Mello, M., Tavares, F., Pereira, N., Gomes Barreto, A.

07-06-2022

J Chromatogr A

https://pubmed.ncbi.nlm.nih.gov/35696843

Praziquantel (PZQ) is an anthelmintic chiral pharmaceutical utilized in schistosomiasis treatment, commonly sold as a racemate, whose primary active molecule is the enantiomer L-(-)-PZQ. The development of new pharmaceutical formulations contenting L-(-)-PZQ has mobilized worldwide efforts from the academy and private companies. Several processes have been proposed to produce pure L-(-)-PZQ, including racemate resolution by preparative chromatography. The design of complex chromatographic processes such as SMB requires accurate information about the adsorption isotherm models and other system parameters and well-quantified uncertainties. We obtained the adsorption isotherms of both PZQ enantiomers using the Frontal Analysis (FA) technique. The associated uncertainties and model confidence bands were calculated from Fisherian and Bayesian approaches. Parameter uncertainties from both methods presented reasonable agreement. Bayesian inference allowed calculating conservative confidence intervals for the parameters, the isotherm curves and the experimental profiles related to FA. Predicted confidence intervals varied from 5.6% to 14% for parameters, 3.9% to 7.1% for the isotherms and 2.02% to 2.22% for the concentration on FA profiles. The estimated nuisance factor agreed with the experimental relative standard deviation and could be applied to predict experimental variances when the same is absent.

A study on the bio-responses of a freshwater snail (Biomphalaria alexandrina) to fungal derived compounds.

Mekawey, A., A R, S., Yosri, M.

10-06-2022

Recent Adv Antiinfect Drug Discov

https://doi.org/10.2174/2772434417666220610110226

Background: Biomphalaria alexandrina snails, as transitional hosts of schistosomiasis, plays an essential part in spread of the illness. Control of these snails by the substance molluscicides antagonistically influences the oceanic climate, causing poisonous and cancer-causing consequences for non-target life forms. **Objective:** Looking for new naturally safe substances can be used for treatment of schistosomiasis disease with minimal side effects on environment and plants, fish wealth and did not affect on human vital functions. **Methods:** Fifty fungal species were used to evaluate their activity against Biomphalaria alexandrina. Study the effect of fungal extract on vital functions of Biomphalaria alexandrina and fish wealth. Purification of active substances and identification of their chemical structures. **Results:** Cladosporium nigrellum and Penicillium aurantiogresium metabolites were effective against B. alexandrina snails, the effects of promising fungal extracts sub-lethal concentrations (IC10 & IC25) on the levels of steroid sex hormones, liver enzymes, total protein, lipids, albumin and glucose were determined. Chemical analyses of this filtrate resulted in the separation of a compound effective against snails; it was identified. Protein electrophoresis showed that fungal filtrate affects the protein pattern of snails' haemolymph. Little or no mortality of Daphnia pulex individuals was observed after their exposure to sub lethal concentrations of each treatment. **Conclusion:** Certain compounds from fungal cultures could be safely used for biological control of Biomphalaria alexandrina snails.

Global analysis of neuropeptides in cestodes identifies Attachin, a SIFamide homolog, as a stimulant of parasite motility and attachment.

Preza, M., Van Bael, S., Temmerman, L., Guarnaschelli, I., Castillo, E., Koziol, U.
11-06-2022
J Neurochem
https://doi.org/10.1111/jnc.15654

Many anthelmintics target the neuromuscular system, in particular by interfering with signalling mediated by classical neurotransmitters. Although peptidergic signalling has been proposed as a novel target for anthelmintics, current knowledge of the neuropeptide complement of many helminth groups is still limited, especially for parasitic flatworms (cestodes, trematodes and monogeneans). In this work, we have characterised the neuropeptide complement of the model cestode Hymenolepis microstoma. Peptidomic characterization of adults of H. microstoma validated many of the neuropeptide precursor (npp) genes previously predicted in silico, and identified novel neuropeptides that are conserved in parasitic flatworms. Most neuropeptides from parasitic flatworms lack significant similarity to those from other animals, confirming the uniqueness of their peptidergic signalling. Analysis of gene expression of ten npp genes by in situ hybridization confirmed that all of them are expressed in the nervous system and identified cryptic features, including the first evidence of dorsoventral asymmetry, as well as a new population of peripheral peptidergic cells that appears to be conserved in the trematode Schistosoma mansoni. Finally, we characterised in greater detail Attachin, an SIFamide homolog. Although its expression is largely restricted to the longitudinal nerve cords and cerebral commissure in H. microstoma, it shows widespread localization in the larval nervous system of Echinococcus multilocularis and Mesocestoides corti. Exogenous addition of a peptide corresponding to the highly conserved C-terminus of Attachin stimulated motility and attachment of M. corti larvae. Altogether, this work provides a robust experimental foothold for the characterization of peptidergic signalling in parasitic flatworms.

This 'mite' be a contaminant.

Coulibaly, J., Bogoch, I.
09-06-2022
J Travel Med
https://pubmed.ncbi.nlm.nih.gov/35678646

High schistosomiasis-related mortality in Northeast Brazil: trends and spatial patterns.

Silva, B., Ferreira, A., Silva, J., Amorim, R., Domingues, A., Pinheiro, M., Bezerra, F., Heukelbach, J., Ramos, A.
06-06-2022
Rev Soc Bras Med Trop
https://pubmed.ncbi.nlm.nih.gov/35674559

Background: We analyzed the trends and spatial patterns of schistosomiasis-related mortality in Northeast Brazil in 2000-2019. **Methods:** A mixed population-based ecological study was conducted, using information on the underlying or associated causes of death. We used Joinpoint regression analysis to calculate the trends. The spatial analysis included rates, spatial moving averages, and standardized mortality rates. The spatial dependence analysis was based on Getis-Ord's G and Gi* indices (Gi star) and local Moran's index to check for autocorrelation. **Results:** A total of 5,814,268 deaths were recorded, of which 9,276 (0.16%) were schistosomiasis-related; 51.0% (n=4,732, adjusted rate 0.90/100,000 inhabitants [95% confidence interval (CI) 0.88-0.93]) were males; 40.0% (n=3,715, adjusted rate 7.40/100.000 inhabitants [95%CI: 7.16-7.64]) were ≥70 years old; 54.8% (n=5,087, crude rate 0.80/100,000 inhabitants) were of mixed/Pardo-Brazilian ethnicity; and 77.9% (n=7,229, adjusted rate 0.86/100,000 inhabitants [95%CI: 0.84-0.88]) lived outside state capitals. The highest proportion of deaths was in the state of Pernambuco (53.9%, n=4,996, adjusted rate 2.72/100,000 inhabitants [95%CI: 2.64-2.79]). Increasing mortality rate was verified in the state of Sergipe. On the coast of the state of Rio Grande do Norte and Bahia, there was spatial dependence of spatio-temporal risk patterns with clusters. Throughout the study period, we found positive spatial autocorrelation and cluster formation. **Conclusions:** In Northeast Brazil, schistosomiasis persists with a high mortality rate, especially in the coastal region, with heterogeneous spatial and temporal patterns. To eliminate schistosomiasis by

2030, it is necessary to strengthen the financing and management of the unified health system (SUS).

Serological evaluation of the schistosome's secretory enzyme phytochelatin synthase and phosphoglycerate mutase for the detection of human Schistosoma japonicum infection.

Angeles, J., Goto, Y., Trinh, M., Rivera, P., Villacorte, E., Kawazu, S.
08-06-2022
Parasitol Res
https://doi.org/10.1007/s00436-022-07568-7

Secretory enzymes from Schistosoma japonicum are promising candidate antigens in the diagnosis of schistosomiasis. Our previous studies have proven that thioredoxin peroxidase-1 (SjTPx-1) is useful for the detection of this parasitic disease in humans, water buffaloes, and dogs. In this study, we evaluated two more secretory enzymes namely phosphoglycerate mutase (SjPGM) and phytochelatin synthase (SjPCS) with SjTPx-1 as the reference antigen. SjPGM was shown to have good diagnostic potentials in animal samples in previous studies, whereas SjPCS was chosen because of its absence in the mammalian hosts. Serum samples including 96 endemic negative controls, 107 schistosomiasis japonica positive samples, and 31 samples positive for other parasitic trematode infections (Clonorchis sinensis, Opisthorchis viverrini, Paragonimus westermani) were tested with the antigens using enzyme-linked immunosorbent assay. Results showed that SjPCS detected more positive samples and had fewer cross-reactions than SjPGM. With 85.05% sensitivity and 93.55% specificity, SjPCS can therefore be used in the detection of human schistosomiasis.

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

Mapping the global distribution of Strongyloides stercoralis and hookworms by ecological niche modeling.

Fleitas, P., Kehl, S., Lopez, W., Travacio, M., Nieves, E., Gil, J., Cimino, R., Krolewiecki, A.
08-06-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05284-w

Background: The WHO has established a control strategy for Strongyloides stercoralis in school-aged children as well as targets and to maintain control programs for Ascaris lumbricoides, Trichuris trichiura and hookworms. For an efficient development of control programs, it is necessary to know the target countries around the world, as well as the areas within each country where efforts should be focused. Therefore, maps that provide information on the areas at risk for soil-transmitted helminth (STH) infections on a national and sub-national scale would allow for a better allocation of resources. Methods: We used the ecological niche models MaxEnt and Kuenm R library to estimate the global distribution of S. stercoralis and hookworms. We used occurrence points of both species extracted from surveys of two literature reviews and from the Global Atlas of Helminth Infection database, together with 14 raster maps of environmental variables. Results: We obtained two raster maps with the presence probability of S. stercoralis and hookworm infections at a global level and then estimated the global population at risk to be 2.6 and 3.4 billion, respectively. The population at risk was also estimated at the country level using estimations for areas as small as 25 km^2. A relationship was found between the probability of the presence of S. stercoralis and its prevalence, and a raster map was generated. Annual precipitation, annual temperature, soil carbon content and land cover were the main associated environmental variables. The ecological niches of Strongyloides stercoralis and hookworms had an overlap of 68%. Conclusions: Here we provide information that can be used for developing more efficient and integrated control strategies for S. stercoralis and hookworm infections. This information can be annexed to the study of other risk factors or even other diseases to assess the health status of a community. GRAPHICAL ABSTARCT.

Clinical helminth infections alter host gut and saliva microbiota.

Gobert, G., Atkinson, L., Lokko, A., Yoonuan, T., Phuphisut, O., Poodeepiyasawat, A., Homsuwan, N., Mousley, A., Adisakwattana, P.
08-06-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010491

Background: Previous reported show altered gut bacterial profiles are associated with helminth infected individuals. Our recently published molecular survey of clinical helminthiases in Thailand border regions demonstrated a more comprehensive picture of infection prevalence when Kato Katz microscopy and copro-qPCR diagnostics were combined. We revealed that Opisthorchis viverrini, hookworm, Ascaris lumbricoides and Trichuris trichiura were the most predominant helminth infections in these regions. In the current study, we have profiled the faecal and saliva microbiota of a subset of these helminth infected participants, in order to determine if microbial changes are associated with parasite infection. Methods: A subset of 66 faecal samples from Adisakwattana et al., (2020) were characterised for bacterial diversity using 16S rRNA gene profiling. Of these samples a subset of 24 participant matched saliva samples were also profiled for microbiota diversity. Sequence data were compiled, OTUs assigned, and diversity and abundance analysed using the statistical software Calypso. Results: The

data reported here indicate that helminth infections impact on both the host gut and oral microbiota. The profiles of faecal and saliva samples, irrespective of the infection status, were considerably different from each other, with more alpha diversity associated with saliva (p-value≤ 0.0015). Helminth infection influenced the faecal microbiota with respect to specific taxa, but not overall microbial alpha diversity. Conversely, helminth infection was associated with increased saliva microbiota alpha diversity (Chao 1 diversity indices) at both the genus (p-value = 0.042) and phylum (p-value = 0.026) taxa levels, compared to uninfected individuals. Elevated individual taxa in infected individuals saliva were noted at the genus and family levels. Since Opisthorchis viverrini infections as a prominent health concern to Thailand, this pathogen was examined separately to other helminths infections present. Individuals with an O. viverrini mono-infection displayed both increases and decreases in genera present in their faecal microbiota, while increases in three families and one order were also observed in these samples. **Discussion:** In this study, helminth infections appear to alter the abundance of specific faecal bacterial taxa, but do not impact on overall bacterial alpha or beta diversity. In addition, the faecal microbiota of O. viverrini only infected individuals differed from that of other helminth single and dual infections. Saliva microbiota analyses of individuals harbouring active helminth infections presented increased levels of both bacterial alpha diversity and abundance of individual taxa. Our data demonstrate that microbial change is associated with helminthiases in endemic regions of Thailand, and that this is reflected in both faecal and saliva microbiota. To our knowledge, this is the first report of an altered saliva microbiota in helminth infected individuals. This work may provide new avenues for improved diagnostics; and an enhanced understanding of both helminth infection pathology and the interplay between helminths, bacteria and their host.

GALE

The efficacy of sampling strategies for estimating scabies prevalence.

Tellioglu, N., Chisholm, R., McVernon, J., Geard, N., Campbell, P.
09-06-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010456

Background: Estimating community level scabies prevalence is crucial for targeting interventions to areas of greatest need. The World Health Organisation recommends sampling at the unit of households or schools, but there is presently no standardised approach to scabies prevalence assessment. Consequently, a wide range of sampling sizes and methods have been used. As both prevalence and drivers of transmission vary across populations, there is a need to understand how sampling strategies for estimating scabies prevalence interact with local epidemiology to affect the accuracy of prevalence estimates. **Methods:** We used a simulation-based approach to compare the efficacy of different scabies sampling strategies. First, we generated synthetic populations broadly representative of remote Australian Indigenous communities and assigned a scabies status to individuals to achieve a specified prevalence using different assumptions about scabies epidemiology. Second, we calculated an observed prevalence for different sampling methods and sizes. **Results:** The distribution of prevalence in subpopulation groups can vary substantially when the underlying scabies assignment method changes. Across all of the scabies assignment methods combined, the simple random sampling method produces the narrowest 95% confidence interval for all sample sizes. The household sampling method introduces higher variance compared to simple random sampling when the assignment of scabies includes a household-specific component. The school sampling method overestimates community prevalence when the assignment of scabies includes an age-specific component. **Discussion:** Our results indicate that there are interactions between transmission assumptions and surveillance strategies, emphasizing the need for understanding scabies transmission dynamics. We suggest using the simple random sampling method for estimating scabies prevalence. Our approach can be adapted to various populations and diseases.

MORSURES DE SERPENT