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DENGUE, CHIKUNGUNYA ET MALADIE A VIRUS ZIKA

Corona versus Dengue: Distinct Mechanisms for Inhibition of Polyprotein Processing by Antiviral Drugs.

Behnam, M., Klein, C.
24-06-2022
ACS Pharmacol Transl Sci
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Inhibitors interfering with processing of the viral polyprotein are used successfully for the control of extremely important viral pathogens, such as HIV and most recently SARS-CoV-2. This Viewpoint provides a mechanistic evaluation of a promising antiviral lead compound against dengue virus, JNJ-A07, 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)butanoic acid. The antiviral effect of JNJ-A07 appears, in our opinion, to be connected to an interference with the function of the viral protease. The analysis reveals for the first time that antiviral drugs target polyprotein processing not only by direct inhibition, but also by disturbing the native sequence of cleavage events. Implications on the development of broad-spectrum antivirals against flaviviruses are addressed.

Analyzing implementation of public health interventions : a need for rigor, and the challenges of stakeholder involvement

Ridde, V., Carillon, S., Desgrées du Loû, A., Sombié, I.
11-07-2022
Rev Epidemiol Sante Publique
https://pubmed.ncbi.nlm.nih.gov/35835715

Objectives: This article shows how conceptual models can help to develop and evaluate public health interventions. It also reports on the challenges of getting stakeholders involved. Method: The analysis is based on the reflexive approach applied by the authors during their participation in two public health intervention research (PHIR) projects, in France and in Burkina Faso. Results: In Paris, PHIR aimed to enable sub-Saharan immigrants to appropriate the existing means of prevention and sexual health care and to strengthen their empowerment in view of preserving their health. Evaluation was carried out using mixed methods. The intervention process theory is based on Ninacs' conceptual model of individual empowerment. The Consolidated Framework For Implementation Research (CFIR) was mobilized a posteriori to analyze the process. PHIR stemmed from collaboration between a research team and two associations. The different stakeholders were involved in the evaluation process, as were, at certain times, persons in highly precarious situations. In Ouagadougou, a community-based dengue vector control intervention was deployed to address an essential but neglected need. As regards evaluation, we opted for a holistic, mixed method approach (effectiveness and process). The contents of the intervention were determined based on tacit knowledge, a community preference survey and solid evidence. The theoretical framework of the intervention consisted in an eco-biological model of vector control. The implementation analysis combined an internal assessment of implementation fidelity with an external CFIR process analysis. All stakeholders were involved in the evaluation process. Discussion: Analysis confirmed not only the value of process evaluations in PHIR, but also the primordial importance of a rigorous approach. Stakeholder involvement is a major challenge to be addressed early in the planning of RISPs; with this in mind, effective and ethically sound assessment mechanisms need to be drawn up. Interdisciplinary evaluative approaches should be preferred, and the use of justified, relevant, and flexible frameworks is highly recommended. Conclusion: Lessons learned for those wishing to engage in the process evaluation of a public health intervention are hereby presented.

A multiple-target mRNA-LNP vaccine induces protective immunity against experimental multi-serotype DENV in mice.

He, L., Sun, W., Yang, L., Liu, W., Li, J.
11-07-2022
Virol Sin
https://pubmed.ncbi.nlm.nih.gov/35835315

Dengue virus (DENV) is a mosquito-borne virus with a rapid spread to humans, causing mild to potentially fatal illness in hundreds of millions of people each year. Due to the large number of serotypes of the virus, there remains an unmet need to develop protective vaccines for a broad spectrum of the virus. Here, we constructed a modified mRNA vaccine containing envelope domain III (E-DIII) and non-structural protein 1 (NS1) coated with lipid nanoparticles. This multi-target vaccine induced a robust antiviral immune response and increased neutralizing antibody titers that blocked all four types of DENV infection in vitro without significant antibody-dependent enhancement (ADE). In addition, there was more bias for Th1 than Th2 in the exact E-DIII and NS1-specific T cell responses after a single injection. Importantly, intramuscular immunization limited DENV transmission in vivo and eliminated vascular leakage. Our findings highlight that chimeric allogeneic structural and non-structural proteins can be effective targets for DENV vaccine and that they can prevent the further development of congenital DENV syndrome.

Origins of high latitude introductions of Aedes aegypti to Nebraska and Utah during 2019.

Gloria-Soria, A., Faraji, A., Hamik, J., White, G., Amsberry, S., Donahue, M., Buss, B., Pless, E., Cosme, L., Powell, J.
08-07-2022
Infect Genet Evol
https://pubmed.ncbi.nlm.nih.gov/35817397

Aedes aegypti (L.), the yellow fever mosquito, is also an

important vector of dengue and Zika viruses, and an invasive species in North America. Aedes aegypti inhabits tropical and sub-tropical areas of the world and in North America, is primarily distributed throughout the southern US states and Mexico. The northern range of Ae. aegypti is limited by cold winter months and establishment in these areas has been mostly unsuccessful. However, frequent introductions of Ae. aegypti to temperate, non-endemic areas during the warmer months can lead to seasonal activity and disease outbreaks. Two Ae. aegypti incursions were reported in the late summer of 2019 into York, Nebraska and Moab, Utah. These states had no history of established populations of this mosquito and no evidence of previous seasonal activity. We genotyped a subset of individuals from each location at 12 microsatellite loci and ~ 14,000 single nucleotide polymorphic markers to determine their genetic affinities to other populations worldwide and investigate their potential source of introduction. Our results support a single origin for each of the introductions from different sources. Aedes aegypti from Utah likely derived from Tucson, Arizona, or a nearby location. Nebraska specimen results were not as conclusive, but point to an origin from southcentral or southeastern US. In addition to an effective, efficient, and sustainable control of invasive mosquitoes, such as Ae. aegypti, identifying the potential routes of introduction will be key to prevent future incursions and assess their potential health threat based on the ability of the source population to transmit a particular virus and its insecticide resistance profile, which may complicate vector control.

Susceptibility to endemic Aedes-borne viruses among pregnant women in Risaralda, Colombia.

Cardona-Ospina, J., Trujillo, A., Jiménez-Posada, E., Sepúlveda-Arias, J., Tabares-Villa, F., Altieri-Rivera, J., Monsalve, A., Restrepo-Chica, J., Osorio, D., Espinoza, D., Zhu, Y., Castrillón-Spitia, J., Henao-SanMartin, V., Murillo-Garcia, D., Millán, N., Olaya, S., Valencia-Montoya, A., Bedoya-Arias, H., Villamizar-Peña, R., Gutierrez-Ocampo, E., Holguin-Rivera, Y., Cortés-Bonilla, I., Cardona-Trujillo, M., García-Barco, A., Bonilla-Aldana, D., Lagos-Grisales, G., Rodríguez-Morales, A., Collins, M.
08-07-2022
Int J Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35817285

Objective: Aedes-borne viruses (ABV) affect humans on every inhabited continent and frequently cause epidemics. Recent epidemics of chikungunya and Zika viruses highlight that preparedness for future epidemics requires assessment of susceptibility, particularly among high-risk groups. We sought to determine immunity against the three major circulating ABV among pregnant women in an ABV-endemic area of Colombia. Methods: A cross-sectional seroprevalence study was performed, enrolling women presenting to Labor and Delivery. Cord blood and maternal peripheral blood was obtained. IgG seroprevalence to flaviviruses and chikungunya was determined by ELISA. An abbreviated neutralization test was used to estimate the frequency and magnitude of immunity to Zika and four dengue serotypes. Cluster analyses explored epidemiologic factors associated with seroprevalence. Results: Most women exhibited high levels of neutralizing antibodies to one or more ABV; however, nearly 20% were seronegative for flaviviruses. Our research took place after the epidemic peak of the ZIKV outbreak in Colombia in 2016, but only 20% of pregnant women had high levels of Zika-neutralizing antibodies consistent with likely protective immunity to ZIKV. Conclusions: Hence, a high proportion pregnant women in Risaralda remain susceptible to one or more ABV including the teratogenic ZIKV, indicating risk for future epidemics in this region.

Generation of soluble, cleaved, well-ordered, native-like dimers of dengue virus 4 envelope protein ectodomain (sE) suitable for vaccine immunogen design.

Chiranjivi, A., Kumar, D., Kumar, R., Parray, H., Ahmed, S., Kumar, C., Shrivastava, T., Banerjee, M., Prasad, B., Das, S.
09-07-2022
Int J Biol Macromol
https://pubmed.ncbi.nlm.nih.gov/35817240

Dengue virus is transmitted by Aedes mosquitoes and dengue is endemic in many regions of the world. Severe dengue results in complications that may lead to death. Although some vaccine candidates are in clinical trials and one vaccine Dengvaxia, with restricted efficacy, is available, there are currently no specific therapies to completely prevent or treat dengue. The dengue virus structural protein E (envelope) exists as a head-to-tail dimer on mature virus, is targeted by broadly neutralizing antibodies and is suitable for developing vaccine immunogens. Here, we have used a redesigned dengue prME expression construct and immunoaffinity chromatography with conformational/quaternary antibody A11 to purify soluble DENV4 sE(A259C) (E ectodomain) dimers from mammalian expression system to ~99 % purity. These dimers retain glycosylation reported for native DENV E, display the three major broadly neutralizing antibody epitopes, and form well-ordered structure. This strategy can be used for developing subunit vaccine candidates against dengue and other flaviviruses.

Exotic viral hepatitis; a review on epidemiology, pathogenesis, and treatment.

Revue de littérature

van Leeuwen, L., de Jong, W., Doornekamp, L., van Gorp, E., Wismans, P., Goeijenbier, M.
08-07-2022
J Hepatol
https://pubmed.ncbi.nlm.nih.gov/35817222

Certain "exotic" viruses are known to cause clinical diseases with potential liver involvement. These include viruses, outside the scope of regular hepatotropic viruses (hepatitis A, -B(D), -C, -E, CMV, EBV), that can be found in (sub)tropical areas causing "exotic viral hepatitis". Transmission routes are mostly arthropod born (Crimean Congo haemorrhagic fever,

dengue, Rift Valley fever, yellow fever). However, others are transmitted by the aerosolised excreta of rodents (Hantavirus, Lassa fever), or via direct contact or contact with bodily fluids (Ebola). Although some exotic viruses are known for their high fatality rate, such as Ebola for example, the clinical presentation of most exotic viruses can range from mild flu-like symptoms, as in most cases, right through to being potentially fatal. A smaller percentage of people develop severe disease with haemorrhagic fever, possibly with (fulminant) hepatitis. Liver involvement is often caused by direct tropism for hepatocytes and Kupffer cells, resulting in virus-mediated and/or immune-mediated necrosis. In all exotic hepatitis viruses, PCR is the most sensitive diagnostic method. The determination of IgM/IgG antibodies is a reasonable alternative, but cross-reactivity can be a problem in the case of flaviviruses. Licenced vaccines are available for yellow fever and Ebola, and they are currently under development for dengue. Therapy for exotic viral hepatitis is predominantly supportive. To ensure that preventive measures can be introduced to control possible outbreaks, the timely detection of these viruses is very important.

Estimating dengue transmission intensity from serological data: A comparative analysis using mixture and catalytic models.

Cox, V., O'Driscoll, M., Imai, N., Prayitno, A., Hadinegoro, S., Taurel, A., Coudeville, L., Dorigatti, I.
11-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010592

Background: Dengue virus (DENV) infection is a global health concern of increasing magnitude. To target intervention strategies, accurate estimates of the force of infection (FOI) are necessary. Catalytic models have been widely used to estimate DENV FOI and rely on a binary classification of serostatus as seropositive or seronegative, according to pre-defined antibody thresholds. Previous work has demonstrated the use of thresholds can cause serostatus misclassification and biased estimates. In contrast, mixture models do not rely on thresholds and use the full distribution of antibody titres. To date, there has been limited application of mixture models to estimate DENV FOI. Methods: We compare the application of mixture models and time-constant and time-varying catalytic models to simulated data and to serological data collected in Vietnam from 2004 to 2009 (N ≥ 2178) and Indonesia in 2014 (N = 3194). Results: The simulation study showed larger mean FOI estimate bias from the time-constant and time-varying catalytic models (-0.007 (95% Confidence Interval (CI): -0.069, 0.029) and -0.006 (95% CI -0.095, 0.043)) than from the mixture model (0.001 (95% CI -0.036, 0.065)). Coverage of the true FOI was > 95% for estimates from both the time-varying catalytic and mixture model, however the latter had reduced uncertainty. When applied to real data from Vietnam, the mixture model frequently produced higher FOI and seroprevalence estimates than the catalytic models. Conclusions: Our results suggest mixture models represent valid, potentially less biased, alternatives to catalytic models, which could be particularly useful when estimating FOI from data with largely overlapping antibody titre distributions.

Recent trends and advancements in electrochemiluminescence biosensors for human virus detection.

Revue de littérature

Sobhanie, E., Salehnia, F., Xu, G., Hamidipanah, Y., Arshian, S., Firoozbakhtian, A., Hosseini, M., Ganjali, M., Hanif, S.
05-07-2022
Trends Analyt Chem
https://doi.org/10.1016/j.trac.2022.116727

Researchers are constantly looking to find new techniques of virus detection that are sensitive, cost-effective, and accurate. Additionally, they can be used as a point-of-care (POC) tool due to the fact that the populace is growing at a quick tempo, and epidemics are materializing greater often than ever. Electrochemiluminescence-based (ECL) biosensors for the detection of viruses have become one of the most quickly developing sensors in this field. Thus, we here focus on recent trends and developments of these sensors with regard to virus detection. Also, quantitative analysis of various viruses (e.g., Influenza virus, SARS-CoV-2, HIV, HPV, Hepatitis virus, and Zika virus) with a specific interest in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was introduced from the perspective of the biomarker and the biological receptor immobilized on the ECL-based sensors, such as nucleic acids-based, immunosensors, and other affinity ECL biosensors.

Lateral flow assays for viruses diagnosis: Up-to-date technology and future prospects.

Revue de littérature

Ince, B., Sezgintürk, M.
05-07-2022
Trends Analyt Chem
https://doi.org/10.1016/j.trac.2022.116725

Bacteria, viruses, and parasites are harmful microorganisms that cause infectious diseases. Early detection of diseases is critical to prevent disease transmission and provide epidemic preparedness, as these can cause widespread deaths and public health crises, particularly in resource-limited countries. Lateral flow assay (LFA) systems are simple-to-use, disposable, inexpensive diagnostic devices to test biomarkers in blood and urine samples. Thus, LFA has recently received significant attention, especially during the pandemic. Here, first of all, the design principles and working mechanisms of existing LFA methods are examined. Then, current LFA implementation strategies are presented for communicable disease diagnoses, including COVID-19, zika and dengue, HIV, hepatitis, influenza, malaria, and other pathogens. Furthermore, this review focuses on an overview of current problems and accessible solutions in detecting infectious agents and diseases by LFA, focusing on increasing sensitivity with various detection methods. In addition, future trends in LFA-based diagnostics are envisioned.

COVID-19 serum can be cross-reactive and neutralizing against Dengue virus (DV) as observed by DV neutralization test.

Nath, H., Mallick, A., Roy, S., Kayal, T., Ranjan, S., Sengupta, S., Sukla, S., Biswas, S.
07-07-2022
Int J Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35811081

Objectives: Observing the serological cross-reactivity between SARS-CoV-2 and dengue virus (DV), we aimed to elucidate its effect in dengue serodiagnosis and infectivity in a highly dengue endemic city of India. Methods: Fifty-two COVID-19 (RT-PCR positive) serum samples were tested in rapid lateral flow immunoassays and DV IgG ELISA to detect DV or SARS-CoV-2 IgG/IgM. The COVID-19 antibody (Ab) positive samples were subjected to virus neutralization test (VNT) (Huh7 cells) using DV type 1 clinical isolate. Results: Majority (93%) of SARS-CoV-2 Ab-positive serum samples cross-reacted with DV in rapid or ELISA tests. All were DV RNA and NS1 antigen negative. COVID-19 serum samples that were DV cross-reactive neutralized DV1. Of these, 57% had no evidence of DV pre-exposure (DV NS1 Ab-negative). Computational study also supported potential interactions between SARS-CoV-2 Ab and DV1. Conclusions: DV serodiagnosis will be inconclusive in areas co-endemic for both the viruses. COVID-19 pandemic appears to impart a protective response against DV in DV-endemic populations.

Sero-epidemiological study of arbovirus infection following the 2015-2016 Zika virus outbreak in Cabo Verde.

Ward, D., Gomes, A., Tetteh, K., Sepúlveda, N., Gomez, L., Campino, S., Clark, T.
09-07-2022
Sci Rep
https://doi.org/10.1038/s41598-022-16115-4

In November 2015, cases of Zika virus infection were recorded in Cabo Verde (Africa), originating from Brazil. The outbreak subsided after seven months with 7580 suspected cases. We performed a serological survey (n=431) in Praia, the capital city, 3 months after transmission ceased. Serum samples were screened for arbovirus antibodies using ELISA techniques and revealed seroconverted individuals with Zika (10.9%), dengue (1-4) (12.5%), yellow fever (0.2%) and chikungunya (2.6%) infections. Zika seropositivity was predominantly observed amongst females (70%). Using a logistic model, risk factors for increased odds of Zika seropositivity included age, self-reported Zika infection, and dengue seropositivity. Serological data from Zika and dengue virus assays were strongly correlated (Spearman's r_s=0.80), which reduced when using a double antigen binding ELISA (Spearman's r_s=0.54). Overall, our work improves an understanding of how Zika and other arboviruses have spread throughout the Cabo Verde population. It also demonstrates the utility of serological assay formats for outbreak investigations.

Flaviviruses hijack the host microbiota to facilitate their transmission.

Gul, L., Korcsmaros, T., Hall, N.
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Cell
https://pubmed.ncbi.nlm.nih.gov/35803242

Flaviviruses, such as Dengue and Zika viruses, infect millions of people worldwide using mosquitos as vectors. In this issue of Cell, Zhang et al. reveal how these viruses manipulate the skin microbiome of infected hosts in a way that increases vector recruitment and viral spread. They propose vitamin A as a way to counteract the virus and decrease transmission.

Potential impact of SARS COV-2 infection on the performance of serological assays used to diagnose arboviral diseases.

Gounassegarane, D., Gunalan, A., Jamir, I., Sharmila, F., Barathidasan, R., Raj, R., Dhodapkar, R.
04-07-2022
J Immunol Methods
https://pubmed.ncbi.nlm.nih.gov/35798263

Background: The COVID-19 pandemic caused by SARS-CoV-2 was first described in December 2019, in China. In addition, there has also been an increase in arboviral infections in recent years. As both infections have similar symptoms, misdiagnosis may occur if both outbreaks occur at the same time. Objective: Our objective was to assess the potential impact of SARS-CoV-2 infection on diagnostic assays used for arboviral diseases. Materials and methods: We conducted this study by testing samples obtained during the precovid phase (before November 2019) and during the covid period (after February 2020). Samples were further grouped as those with acute febrile illness (AFI) and those without. All samples were tested for anti SARS-CoV-2 Ab, Chikungunya and Dengue specific IgM antibodies to evaluate potential serological cross-reactions between COVID-19 and Arbovirus specific antibodies. Results: One sample from the 62 cases of AFI during the pre-covid phase showed seropositivity for SARS-CoV-2 antibodies. Also, in asymptomatic individuals, arboviral seropositivity was significantly higher in the COVID period samples (22%) compared to pre-COVID samples (3%). Conclusion: Due to similar clinical symptoms and cross reactions in both infections, relying solely on serological testing for arboviral diagnosis may be less sensitive; other clinical and laboratory parameters may be required.

The timing setting in kinetic dengue studies: A systematic review.

Revue de littérature

Tran, L., Tuan, N., Tam, D., Alshareef, A., Emad, E., Khalifa, A., Hieu, T., Khan, Z., Jun, L., Hirayama, K., Huy, N.
04-07-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35798088

Dengue is classified as an endemic infectious disease, which is transmitted by Aedes mosquitos. Kinetic studies, which monitor the viral load of the disease, have been the mainstay for several decades in humanity's quest to control this disease. Our study aims to systematically evaluate the usage of different timing systems in dengue kinetic studies. A search in nine electronic databases and manual search of reference and citation lists were conducted to find relevant studies. A quality assessment using the National Institute of Health tools for observational cohort and cross-sectional studies was performed. The protocol was registered in PROSPERO with number CRD42018086435. As results, among included 87 studies, 71 studies (81.6%) use a timing system which is based on the day of illness onset, of which, 11 studies designate the day of illness onset as "day 0″ (type 1A) while 60 studies designate it as "day 1″ (type 1B). Only ten articles (11.5%) designate the day of defervescence as "day 0″, the day before and after defervescence as "day -1″ and "day +1″, respectively. Four articles (4.6%) use a timing system based on the day of hospital admission. Lastly, two studies (2.3%) designate the day of hemorrhagic manifestation as "day 0″ and two studies (2.3%) designate the day of pharmacological treatment as "day 1″. Therefore, the timing system which designates the day of illness onset as "day 1″ (type 1B) was most commonly used. Inconsistent definitions of "day 0″ and "day 1″ may lead to disparities in results across the studies and may have a negative impact on treatment guidelines implementation.

Milk exosomes elicit a potent anti-viral activity against dengue virus.

Yenuganti, V., Afroz, S., Khan, R., Bharadwaj, C., Nabariya, D., Nayak, N., Subbiah, M., Chintala, K., Banerjee, S., Reddanna, P., Khan, N.
06-07-2022
J Nanobiotechnology
https://doi.org/10.1186/s12951-022-01496-5

Background: Exosomes are nano-sized vesicles secreted by various cells into the intra and extracellular space and hence is an integral part of biological fluids including milk. In the last few decades, many research groups have proved the potential of milk exosomes as a sustainable, economical and non-immunogenic drug delivery and therapeutic agent against different pathological conditions. However, its anti-viral properties still remain to be unearthed. Methods: Here, we have been able to isolate, purify and characterize the milk derived exosomes from Cow (CME) and Goat (GME) and further studied its antiviral properties against Dengue virus (DENV), Newcastle Disease Virus strain Komarov (NDV-K) and Human Immunodeficiency Virus (HIV-1) using an in-vitro infection system. Results: TEM, NTA and DLS analysis validated the appropriate size of the isolated cow and goat milk exosomes (30-150 nm). Real-time PCR and immunoblotting results confirmed the presence of several milk exosomal miRNAs and protein markers. Our findings suggest that GME significantly decreased the infectivity of DENV. In addition, we confirmed that GME significantly reduces DENV replication and reduced the secretion of mature virions. Furthermore, heat inactivation of GME did not show any inhibition on DENV infection, replication, and secretion of mature virions. RNase treatment of GME abrogates the anti-viral properties indicating direct role of exosomes in DENV inhibition. In addition GME inhibited the infectivity of NDV-K, but not HIV-1, suggesting that the GME mediated antiviral activity might be virus specific. Conclusion: This study demonstrates the anti-viral properties of milk exosomes and opens new avenues for the development of exosome-based therapies to treat viral diseases.

First comprehensive analysis of Aedes aegypti bionomics during an arbovirus outbreak in west Africa: Dengue in Ouagadougou, Burkina Faso, 2016-2017.

Badolo, A., Sombié, A., Yaméogo, F., Wangrawa, D., Sanon, A., Pignatelli, P., Sanon, A., Viana, M., Kanuka, H., Weetman, D., McCall, P.
06-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010059

Background: Dengue's emergence in West Africa was typified by the Burkina Faso outbreaks in 2016 and 2017, the nation's largest to date. In both years, we undertook three-month surveys of Aedes populations in or near the capital city Ouagadougou, where the outbreaks were centered. Methodology: In 1200LG (urban), Tabtenga (peri-urban) and Goundry (rural) localities, we collected indoor and outdoor resting mosquito adults, characterized larval habitats and containers producing pupae and reared immature stages to adulthood in the laboratory for identification. All mosquito adults were identified morphologically. Host species (from which bloodmeals were taken) were identified by PCR. Generalized mixed models were used to investigate relationships between adult or larval densities and multiple explanatory variables. Results: From samples in 1,780 houses, adult Ae. aegypti was significantly more abundant in the two urban localities (Tabtenga and 1200 LG) in both years than in the rural site (Goundry), where Anopheles spp. were far more common. Results from adult collections indicated a highly exophilic and anthropophilic (>90% bloodmeals of human origin) vector population, but with a relatively high proportion of bloodfed females caught inside houses. Habitats producing most pupae were waste tires (37% of total pupae), animal troughs (44%) and large water barrels (30%). While Stegomyia indices were not reliable indicators of adult mosquito abundance, shared influences on adult and immature stage densities included rainfall and container water level, collection month and container type/purpose. Spatial analysis showed autocorrelation of densities, with a partial overlap in adult and immature stage hotspots. Conclusion: Results provide an evidence base for the selection of appropriate vector control methods to minimize the risk, frequency and magnitude of future outbreaks in Ouagadougou. An integrated strategy combining community-driven practices, waste disposal and insecticide-based interventions is proposed. The prospects for

developing a regional approach to arbovirus control in West Africa or across Africa are discussed.

Zika virus-like particle vaccine fusion loop mutation increases production yield but fails to protect AG129 mice against Zika virus challenge.

Thompson, D., Guenther, B., Manayani, D., Mendy, J., Smith, J., Espinosa, D., Harris, E., Alexander, J., Vang, L., Morello, C.
06-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010588

Zika virus (ZIKV) is a mosquito-borne flavivirus with maternal infection associated with preterm birth, congenital malformations, and fetal death, and adult infection associated with Guillain-Barré syndrome. Recent widespread endemic transmission of ZIKV and the potential for future outbreaks necessitate the development of an effective vaccine. We developed a ZIKV vaccine candidate based on virus-like-particles (VLPs) generated following transfection of mammalian HEK293T cells using a plasmid encoding the pre-membrane/membrane (prM/M) and envelope (E) structural protein genes. VLPs were collected from cell culture supernatant and purified by column chromatography with yields of approximately 1-2mg/L. To promote increased particle yields, a single amino acid change of phenylalanine to alanine was made in the E fusion loop at position 108 (F108A) of the lead VLP vaccine candidate. This mutation resulted in a modest 2-fold increase in F108A VLP production with no detectable prM processing by furin to a mature particle, in contrast to the lead candidate (parent). To evaluate immunogenicity and efficacy, AG129 mice were immunized with a dose titration of either the immature F108A or lead VLP (each alum adjuvanted). The resulting VLP-specific binding antibody (Ab) levels were comparable. However, geometric mean neutralizing Ab (nAb) titers using a recombinant ZIKV reporter were significantly lower with F108A immunization compared to lead. After virus challenge, all lead VLP-immunized groups showed a significant 3- to 4-Log10 reduction in mean ZIKV RNAemia levels compared with control mice immunized only with alum, but the RNAemia reduction of 0.5 Log10 for F108A groups was statistically similar to the control. Successful viral control by the lead VLP candidate following challenge supports further vaccine development for this candidate. Notably, nAb titer levels in the lead, but not F108A, VLP-immunized mice inversely correlated with RNAemia. Further evaluation of sera by an in vitro Ab-dependent enhancement assay demonstrated that the F108A VLP-induced immune sera had a significantly higher capacity to promote ZIKV infection in FcγR-expressing cells. These data indicate that a single amino acid change in the fusion loop resulted in increased VLP yields but that the immature F108A particles were significantly diminished in their capacity to induce nAbs and provide protection against ZIKV challenge.

City puzzles: Does urban land scape affect genetic population structure in Aedes aegypti?

Maffey, L., Confalonieri, V., Hasson, E., Schweigmann, N.
06-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010549

Cities usually offer a suitable environment for the dengue vector Aedes aegypti, providing oviposition sites, accessibility to human hosts and nectar meals. However, large urban centres are highly heterogeneous environments, forming a patched landscape that could affect Ae. aegypti population dynamics and dispersal. Here, we performed a genome-wide analysis using Rad-seq data from 99 Ae. aegypti specimens collected in three areas within Buenos Aires city with varying levels of urbanization/land use: highly urbanized Area 1, intermediate Area 2 and poorly urbanized Area 3. We found an inverse association between urbanization levels and spatial genetic structure. Populations from highly urbanized Area 1 did not present genetic structure whereas two and three clusters were detected in Areas 2 and 3, respectively. In the case of Area 3, initial analyses showed separation in clusters was mostly due to elevated consanguinity within sites although three clusters were still detected after closely related individuals were discarded. Mosquitoes around each site displayed a high degree of isolation, evidencing a close dependence between the vector and human dwellings. Interestingly, specimens from distant boroughs (within the limits of the city) and the city's outskirts formed a single cluster with inner city sites (Area 1), highlighting the role of passive transport in shaping population structure. Genetic distances were poorly correlated with geographic distances in Buenos Aires, suggesting a stronger influence of passive than active dispersal on population structure. Only Area 2 displayed a significant isolation-by-distance pattern ($p = 0.046$), with males dispersing more than females ($p = 0.004$ and $p = 0.016$, respectively). Kinship analyses allowed us to detect full-siblings located 1.5 km apart in Area 1, which could be due to an extreme event of active female dispersal. Effective population size was higher in Area 2 confirming that cemeteries represent highly favourable environments for Ae. aegypti and need to be specifically targeted. Our results suggest that control programs should take into account urban landscape heterogeneity in order to improve vector control.

Zika virus alters centrosome organization to suppress the innate immune response.

Kodani, A., Knopp, K., Di Lullo, E., Retallack, H., Kriegstein, A., DeRisi, J., Reiter, J.
06-07-2022
EMBO Rep
https://doi.org/10.15252/embr.202052211

Zika virus (ZIKV) is a flavivirus transmitted via mosquitoes and sex to cause congenital neurodevelopmental defects, including microcephaly. Inherited forms of microcephaly (MCPH) are associated with disrupted centrosome organization. Similarly, we found that ZIKV infection disrupted centrosome organization. ZIKV infection disrupted the organization of centrosomal proteins including CEP63, a

MCPH-associated protein. The ZIKV nonstructural protein NS3 bound CEP63, and expression of NS3 was sufficient to alter centrosome architecture and CEP63 localization. Loss of CEP63 suppressed ZIKV-induced centrosome disorganization, indicating that ZIKV requires CEP63 to disrupt centrosome organization. ZIKV infection or CEP63 loss decreased the centrosomal localization and stability of TANK-binding kinase 1 (TBK1), a regulator of the innate immune response. ZIKV infection also increased the centrosomal accumulation of the CEP63 interactor DTX4, a ubiquitin ligase that degrades TBK1. Therefore, we propose that ZIKV disrupts CEP63 function to increase centrosomal DTX4 localization and destabilization of TBK1, thereby tempering the innate immune response.

CDK4/6 inhibition enhances oncolytic virus efficacy by potentiating tumor-selective cell killing and T cell activation in refractory glioblastoma.

Guo, D., Xiao, J., Liang, J., Fan, J., Hou, P., Li, X., Zhang, H., Li, K., Bu, L., Li, P., He, M., Zhong, Y., Guo, L., Jia, P., Xiao, Q., Wu, J., Peng, H., Li, C., Xing, F.
06-07-2022
Cancer Res
https://pubmed.ncbi.nlm.nih.gov/35792620

Glioblastoma multiforme (GBM) is among the most aggressive human cancers. Although oncolytic virus (OV) therapy has been proposed as a potential approach to treat GBM, it frequently fails because GBM cells are usually nonpermissive to OV. Here, we describe a dual-step drug screen for identifying chemical enhancers of oncolytic virus in GBM. From a high-throughput screen of 1416 FDA-approved drugs, an inhibitor of CDK4/6 was identified as the top enhancer, selectively increasing potency of two OV strains, VSVΔ51 and Zika virus. Mechanistically, CDK4/6 inhibition promoted autophagic degradation of MAVS, resulting in impaired antiviral responses and enhanced tumor-selective replication of VSVΔ51 in vitro and in vivo. CDK4/6 inhibition cooperated with VSVΔ51 to induce severe DNA damage stress and amplify oncolysis. In GBM xenograft models, combined treatment with CDK4/6 inhibitor and VSVΔ51 significantly inhibited tumor growth and prolonged the survival of tumor-bearing mice. Further investigation revealed that CDK4/6 inhibitor and VSVΔ51 synergistically induced immunogenic cell death and boosted anti-tumor immunity. Together, this study features a promising approach of treating aggressive GBM through the combination of CDK4/6 inhibitor with OV.

The main component of the scent of *Senecio madagascariensis* flowers is an attractant for *Aedes aegypti* (L.) (Diptera: Culicidae) mosquitoes.

Kashiwagi, G., von Oppen, S., Harburguer, L., González-Audino, P.
06-07-2022
Bull Entomol Res
https://doi.org/10.1017/S0007485322000256

Aedes aegypti (L.) (Diptera: Culicidae) is one of the main vectors of arboviruses, including dengue, Zika, and chikungunya. It almost exclusively inhabits urban areas. Both sexes feed on plant carbohydrates, although for males, this is their only food source. In the case of floral nectars, mosquitoes locate plant sugar sources assisted by volatile compounds. In this work, we found that the floral scent of *Senecio madagascariensis* elicited a behavioral response in males; therefore, we focused on identifying the volatiles emitted by these flowers. The terpenes (±)-α-pinene, β-pinene, sabinene, and phellandrene and 1-alkenes 1-undecene, and 1-nonene were identified. To determine which compounds are bioactive, pure synthetic lures were assessed using an olfactometer. Only the main compound 1-nonene was an attractant for males. Since our goal was the introduction of synthetic floral-based attractants in toxic sugar-baited traps, we formulated 1-nonene in solid paraffin and stearin matrices to obtain a controlled release system. The bioassay with a toxicological end point showed that the incorporation of a feeding attractant to the toxic sugar trap increased overall mortality. These results suggest that it is possible to use plant volatile compounds or flower cuttings as male *Ae. aegypti* attractants to improve the efficacy of baited traps.

Postoperative dengue haemorrhagic shock and Trichosporon fungal sepsis: a multidisciplinary rescue.

Sachan, A., Nayyar, R., Kumar, A., Rewari, V.
05-07-2022
BMJ Case Rep
https://pubmed.ncbi.nlm.nih.gov/35790323

A woman in her 30s had robotic pyeloplasty done for right ureteropelvic junction obstruction. Incidentally she developed dengue viral fever starting on postoperative day 1 itself, which progressed to dengue haemorrhagic shock by 1 week, complicating pyeloplasty due to pelvicalyceal haematoma. Dengue associated shock was superimposed with subsequent gram-negative bacterial sepsis, further complicated later with Trichosporon fungal sepsis. She was managed under multidisciplinary care, involving urology, infectious disease and ICU care. Her diagnostic and difficult management issues due to these rare sequential medical issues in an otherwise usually uncomplicated postsurgical phase are discussed along with short review of literature. This case highlights the importance of early diagnosis, timely supportive care and appropriate management in such tropical infections with significant associated mortality.

In silico identification and in vitro antiviral validation of potential inhibitors against Chikungunya virus.

Verma, J., Hasan, A., Sunil, S., Subbarao, N.
05-07-2022
J Comput Aided Mol Des
https://doi.org/10.1007/s10822-022-00463-4

The Chikungunya virus (CHIKV) has become endemic in the Africa, Asia and Indian subcontinent, with its continuous re-emergence causing a significant public health crisis. The unavailability of specific antivirals and vaccines against the virus has highlighted an urgent need for novel therapeutics. In the present study, we have identified small molecule inhibitors targeting the envelope proteins of the CHIKV to interfere with the fusion process, eventually inhibiting the cell entry of the virus particles. We employed high throughput computational screening of large datasets against two different binding sites in the E1-E2 dimer to identify potential candidate inhibitors. Among them, four high affinity inhibitors were selected to confirm their anti-CHIKV activity in the in vitro assay. Quercetin derivatives, Taxifolin and Rutin, binds to the E1-E2 dimer at different sites and display inhibition of CHIKV infection with EC_{50} values 3.6 µM and 87.67 µM, respectively. Another potential inhibitor with ID ChemDiv 8015-3006 binds at both the target sites and shows anti-CHIKV activity at EC_{50}=41 µM. The results show dose-dependent inhibitory effects of Taxifolin, Rutin and ChemDiv 8015-3006 against the CHIKV with minimal cytotoxicity. In addition, molecular dynamics studies revealed the structural stability of these inhibitors at their respective binding sites in the E1-E2 protein. In conclusion, our study reports Taxifolin, Rutin and ChemDiv 8015-3006 as potential inhibitors of the CHIKV entry. Also, this study suggests a few potential candidate inhibitors which could serve as a template to design envelope protein specific CHIKV entry inhibitors.

Zika virus persistence in the male macaque reproductive tract.

Ball, E., Pesavento, P., Van Rompay, K., Keel, M., Singapuri, A., Gomez-Vazquez, J., Dudley, D., O'Connnor, D., Breitbach, M., Maness, N., Schouest, B., Panganiban, A., Coffey, L.
05-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010566

Zika virus (ZIKV) is unique among mosquito-borne flaviviruses in that it is also vertically and sexually transmitted by humans. The male reproductive tract is thought to be a ZIKV reservoir; however, the reported magnitude and duration of viral persistence in male genital tissues vary widely in humans and non-human primate models. ZIKV tissue and cellular tropism and potential effects on male fertility also remain unclear. The objective of this study was to resolve these questions by analyzing archived genital tissues from 51 ZIKV-inoculated male macaques and correlating data on plasma viral kinetics, tissue tropism, and ZIKV-induced pathological changes in the reproductive tract. We hypothesized that ZIKV would persist in the male macaque genital tract for longer than there was detectable viremia, where it would localize to germ and epithelial cells and associate with lesions. We detected ZIKV RNA and infectious virus in testis, epididymis, seminal vesicle, and prostate gland. In contrast to prepubertal males, sexually mature macaques were significantly more likely to harbor persistent ZIKV RNA or infectious virus somewhere in the genital tract, with detection as late as 60 days post-inoculation. ZIKV RNA localized primarily to testicular stem cells/sperm precursors and epithelial cells, including Sertoli cells, epididymal duct epithelium, and glandular epithelia of the seminal vesicle and prostate gland. ZIKV infection was associated with microscopic evidence of inflammation in the epididymis and prostate gland of sexually mature males, pathologies that were absent in uninfected controls, which could have significant effects on male fertility. The findings from this study increase our understanding of persistent ZIKV infection which can inform risk of sexual transmission during assisted reproductive therapies as well as potential impacts on male fertility.

The epidemiology and disease burden of children hospitalized for viral infections within the family Flaviviridae in China: A national cross-sectional study.

Wang, R., Wang, X., Zhang, L., Feng, G., Liu, M., Zeng, Y., Xie, Z.
05-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010562

Background: Viruses of the family Flaviviridae, including Japanese encephalitis virus (JEV), dengue virus (DENV), yellow fever virus (YFV) and hepatitis C virus (HCV), are widely distributed worldwide. JEV, DENV and YFV belong to the genus Flavivirus, whereas HCV belongs to the genus Hepacivirus. Children's symptoms are usually severe. As a result, rates of hospitalization due to infection with these viruses are high. The epidemiology and disease burden of hospitalized children have rarely been described in detail to date. The objective of this study was to report the general epidemiological characteristics, clinical phenotype, length of stay (LOS), burden of disease, and potential risk factors for hospitalized children infected with JEV, DENV, YFV, or HCV in Chinese pediatric hospitals. **Methodology:** A cross-sectional study of epidemiology and disease burden of children hospitalized for Flaviviridae virus infections between December 2015 and December 2020 in China was performed. Face sheets of discharge medical records (FSMRs) were collected from 27 tertiary children's hospitals in the Futang Research Center of Pediatric Development and aggregated into FUTang Update medical REcords (FUTURE). Information on sociodemographic variables, clinical phenotype, and LOS as well as economic burden was included in FSMRs and compared using appropriate statistical tests. **Findings:** The study described 490 children aged 0-15 years hospitalized for infections with Flaviviridae viruses. Japanese encephalitis (JE) cases are the highest, accounting for 92.65% of the total hospitalization cases caused by Flaviviridae virus infection. The incidence of JE peaked from July to October with a profile of a high proportion of severe cases (68.06%) and low mortality (0.44%). Rural children had a significantly higher incidence than urban children (91.63%). Most hospitalized dengue cases were reported in 2019 when dengue outbreaks occurred in many provinces of China, although only 14 dengue cases were collected during the study period. Yellow fever (YF) is still an imported disease in China. The hospitalizations for children

with hepatitis C (HC) were not high, and mild chronic HC was the main clinical phenotype of patients. Among the four viral infections, JE had the highest disease burden (LOS and expenditure) for hospitalized children. **Conclusion:** First, the present study reveals that JE remains the most serious disease due to Flaviviridae virus infection and threatens children's health in China. Many pediatric patients have severe illnesses, but their mortality rate is lower, suggesting that existing treatment is effective. Both JEV vaccination and infection control of rural children should represent a focus of study. Second, although the dual risks of indigenous epidemics and imports of DENV still exist, the prevalence of DENV in children is generally manageable. Third, YFV currently shows no evidence of an epidemic in China. Finally, the proportion of children with chronic hepatitis C (CHC) is relatively large among hospitalized children diagnosed with HCV. Thus, early and effective intervention should be offered to children infected with HCV to ease the burden of CHC on public health.

Development of a next-generation chikungunya virus vaccine based on the HydroVax platform.

Slifka, D., Raué, H., Weber, W., Andoh, T., Kreklywich, C., DeFilippis, V., Streblow, D., Slifka, M., Amanna, I.
05-07-2022
PLoS Pathog
https://doi.org/10.1371/journal.ppat.1010695

Chikungunya virus (CHIKV) is an emerging/re-emerging mosquito-borne pathogen responsible for explosive epidemics of febrile illness characterized by debilitating polyarthralgia and the risk of lethal infection among the most severe cases. Despite the public health risk posed by CHIKV, no vaccine is currently available. Using a site-directed hydrogen peroxide-based inactivation approach, we developed a new CHIKV vaccine, HydroVax-CHIKV. This vaccine technology was compared to other common virus inactivation approaches including β-propiolactone (BPL), formaldehyde, heat, and ultraviolet (UV) irradiation. Heat, UV, and BPL were efficient at inactivating CHIKV-181/25 but caused substantial damage to neutralizing epitopes and failed to induce high-titer neutralizing antibodies in vaccinated mice. HydroVax-CHIKV and formaldehyde-inactivated CHIKV retained intact neutralizing epitopes similar to live virus controls but the HydroVax-CHIKV approach demonstrated a more rapid rate of virus inactivation. HydroVax-CHIKV vaccination induced high neutralizing responses to homologous and heterologous CHIKV clades as well as to other alphaviruses including Mayaro virus, O'nyong'nyong virus, and Una virus. Following heterologous infection with CHIKV-SL15649, HydroVax-CHIKV-immunized mice were protected against viremia, CHIKV-associated arthritic disease, and lethal CHIKV infection by an antibody-dependent mechanism. In contrast, animals vaccinated with Heat- or UV-inactivated virus showed no protection against viremia in addition to demonstrating significantly exacerbated CD4+ T cell-mediated footpad swelling after CHIKV infection. Together, these results demonstrate the risks associated with using suboptimal inactivation methods that fail to elicit protective neutralizing antibody responses and show that HydroVax-CHIKV represents a promising new vaccine candidate for prevention of CHIKV-associated disease.

Larvicidal Activity of Two Rutaceae Plant Essential Oils and Their Constituents Against Aedes albopictus (Diptera: Culicidae) in Multiple Formulations.

Jian, R., Lin, Y., Li, Y., Wu, W., Ren, X., Liang, Z., Kong, L., Cai, J., Lao, C., Wu, M., Chen, W., Chen, J., Hong, W., Sheng, Z.
04-07-2022
J Med Entomol
https://pubmed.ncbi.nlm.nih.gov/35786778

Aedes albopictus (Skuse) is a vector of several arboviruses, such as dengue, chikungunya, West Nile, and Zika viruses. At present, the use of synthetic insecticides is the main vector control strategy. However, the widespread and long-term use of insecticides has aroused several problems, including insecticide resistance, environmental pollution, and non-target species effects, thereby encouraging researchers to search for new alternatives derived from natural products. In recent decades, essential oils (EOs) as natural alternatives to control mosquitoes have received increasing attention. In the initial larvicidal activity screen, two Rutaceae plants (Citrus aurantium and Citrus paradisi) EOs were selected and evaluated for killing Ae. albopictus larvae. The LC50 values of C. aurantium and C. paradisi EOs against Ae. albopictus were 91.7 and 100.9 ppm, respectively. The main components of C. aurantium EO include diethyl o-phthalate (37.32%), limonene (10.04%), and methyl dihydrojasmonate (6.48%). The main components of C. paradisi EO include limonene (60.51%), diethyl o-phthalate (11.75%), linalool (7.90%), and styralyl acetate (6.28%). Among these main components of the two EOs, limonene showed potent larvicidal activity, with the LC50 value of 39.7 ppm. The nanoemulsions of limonene were prepared and characterized. The duration of larvicidal activity was greater in the limonene nanoemulsions than when limonene was applied in solvent. This study demonstrates that EOs of plants in family Rutaceae are a potential resource to develop new larvicides, and nanoemulsification is an effective method for improving the physicochemical properties and efficacy of natural products as larvicides.

A high-throughput yeast display approach to profile pathogen proteomes for MHC-II binding.

Huisman, B., Dai, Z., Gifford, D., Birnbaum, M.
04-07-2022
Elife
https://doi.org/10.7554/eLife.78589

T cells play a critical role in the adaptive immune response, recognizing peptide antigens presented on the cell surface by Major Histocompatibility Complex (MHC) proteins. While assessing peptides for MHC binding is an important component of probing these interactions, traditional assays for testing peptides of interest for MHC binding are limited in

throughput. Here we present a yeast display-based platform for assessing the binding of tens of thousands of user-defined peptides in a high throughput manner. We apply this approach to assess a tiled library covering the SARS-CoV-2 proteome and four dengue virus serotypes for binding to human class II MHCs, including HLA-DR401, -DR402, and -DR404. While the peptide datasets show broad agreement with previously described MHC-binding motifs, they additionally reveal experimentally validated computational false positives and false negatives. We therefore present this approach as able to complement current experimental datasets and computational predictions. Further, our yeast display approach underlines design considerations for epitope identification experiments and serves as a framework for examining relationships between viral conservation and MHC binding, which can be used to identify potentially high-interest peptide binders from viral proteins. These results demonstrate the utility of our approach to determine peptide-MHC binding interactions in a manner that can supplement and potentially enhance current algorithm-based approaches.

Sec61 Inhibitor Apratoxin S4 Potently Inhibits SARS-CoV-2 and Exhibits Broad-Spectrum Antiviral Activity.

Pohl, M., Martin-Sancho, L., Ratnayake, R., White, K., Riva, L., Chen, Q., Lieber, G., Busnadiego, I., Yin, X., Lin, S., Pu, Y., Pache, L., Rosales, R., Déjosez, M., Qin, Y., De Jesus, P., Beall, A., Yoh, S., Hale, B., Zwaka, T., Matsunaga, N., García-Sastre, A., Stertz, S., Chanda, S., Luesch, H.
29-06-2022
ACS Infect Dis
https://doi.org/10.1021/acsinfecdis.2c00008

There is a pressing need for host-directed therapeutics that elicit broad-spectrum antiviral activities to potentially address current and future viral pandemics. Apratoxin S4 (Apra S4) is a potent Sec61 inhibitor that prevents cotranslational translocation of secretory proteins into the endoplasmic reticulum (ER), leading to anticancer and antiangiogenic activity both in vitro and in vivo. Since Sec61 has been shown to be an essential host factor for viral proteostasis, we tested Apra S4 in cellular models of viral infection, including SARS-CoV-2, influenza A virus, and flaviviruses (Zika, West Nile, and Dengue virus). Apra S4 inhibited viral replication in a concentration-dependent manner and had high potency particularly against SARS-CoV-2 and influenza A virus, with subnanomolar activity in human cells. Characterization studies focused on SARS-CoV-2 revealed that Apra S4 impacted a post-entry stage of the viral life-cycle. Transmission electron microscopy revealed that Apra S4 blocked formation of stacked double-membrane vesicles, the sites of viral replication. Apra S4 reduced dsRNA formation and prevented viral protein production and trafficking of secretory proteins, especially the spike protein. Given the potent and broad-spectrum activity of Apra S4, further preclinical evaluation of Apra S4 and other Sec61 inhibitors as antivirals is warranted.

Modifying mosquitoes to suppress disease transmission: Is the long wait over?

Powell, J.
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Genetics
https://pubmed.ncbi.nlm.nih.gov/35652239

For more than 50years it has been a dream of medical entomologists and public health workers to control diseases like malaria and dengue fever by modifying, through genetics and other methods, the arthropods that transmit them to humans. A brief synopsis of the history of these efforts as applied to mosquitoes is presented; none proved to be effective in reducing disease prevalence. Only in the last few years have novel approaches been developed or proposed that indicate the long wait may be over. Three recent developments are particularly promising: CRISPR-Cas9 driven genetic modification, shifting naturally occurring allele frequencies, and microbe-based modifications. The last is the furthest along in implementation. Dengue fever incidence has been reduced between 40% and 96% in 4 different regions of the world where Wolbachia-infected Aedes aegypti have been established in the field. It is not yet clear how sustainable such control programs will prove to be, but there is good reason for optimism. In light of this, the time is ripe for reinvigorated research on vectors, especially genetics. Vector-borne diseases primarily affect under-developed countries and thus have not received the attention they deserve from wealthier countries with well-developed and funded biomedical research establishments.

RAGE

Limbic system symptoms of rabies infection.

Mohindra, R., Madhav, M., Suri, V., Divyashree, K.
11-07-2022
BMJ Case Rep
https://pubmed.ncbi.nlm.nih.gov/35817494

Rabies is a fatal aggressive disease of the nervous system which predominantly causes motor and autonomic dysfunction. Limbic system involvement has been reported rarely, with limited data on its prevalence. The diagnosis becomes challenging when a patient presents with limbic system involvement in the absence of a clear history of an animal bite. We herein illustrate a case of a young man who presented with recurrent episodes of inappropriate ejaculation. He eventually developed hydrophobia and aerophobia, leading to a diagnosis of rabies. This case emphasises the importance of considering the possibility of rabies encephalitis when a patient presents with symptoms of limbic system involvement since early diagnosis helps in instituting appropriate public health measures and reducing exposure to infection. Furthermore, high-quality intensive care with supportive management is the mainstay of therapy

in such patients until we have novel and effective antiviral drugs for rabies treatment.

Genotyping of rabies positive samples isolated from animals in Mato Grosso and Rondônia - Brazil.

Pimentel, M., Nassarden, S., Cândido, S., Dutra, V., Nakazato, L.
08-07-2022
Infect Genet Evol
https://pubmed.ncbi.nlm.nih.gov/35817398

Lyssavirus is a genus that causes infectious disease transmit by bats transmit, which results in economic losses in livestock and public health problems. From 2005 to 2019, more than 49 thousand cases of the disease were registered in animals in Brazil, with 3418 registered in Mato Grosso (MT). The lack of information on the genetic diversity and distribution of the rabies virus in MT was the motivation for carrying out this study. A total of 117 samples of brain tissue from cattle, horses, donkeys, mules and sheep from 29 municipalities in the state of MT and one municipality in Rondônia were used. Direct immunofluorescence and/or biological tests performed from 2014 to 2021 indicated that all samples were positive for the disease. RNA was extracted and molecular analysis was performed using RT-PCR for the N gene. Of the 117 samples analyzed, 50 were amplified by RT-PCR, purified and sequenced. The samples showed 93.13%-100% identity with the rabies virus. The sequences were submitted to phylogenetic analysis that resulted in a tree of four clades; these were genetically grouped into distinct regions within the Desmodus rotundus lineage. The results of the geolocation of clades will be useful to guide monitoring, control and health surveillance programs in MT.

Nonarboviral Equine Encephalitides.

Revue de littérature

Toribio, R.
07-07-2022
Vet Clin North Am Equine Pract
https://pubmed.ncbi.nlm.nih.gov/35811198

Several viruses transmitted by biological vectors or through direct contact, air, or ingestion cause neurologic disease in equids. Of interest are viruses of the Togaviridae, Flaviviridae, Rhabdoviridae, Herpesviridae, Bornaviridae, and Bunyaviridae families. Variable degree of inflammation is present with these viruses but lack of an inflammatory response does not rule out their presence. The goal of this article is to provide an overview on pathophysiologic and clinical aspects of nonarboviral equine encephalitides, specifically on lyssaviruses (rabies) and bornaviruses (Borna disease).

Effect of inhibition of Toll-like receptor 3 signaling on pathogenesis of rabies virus in mouse model.

Sardana, S., Singh, K., Saminathan, M., Vineetha, S., Panda, S., Dinesh, M., Maity, M., Varshney, R., Sulabh, S., Sahoo, M., Dutt, T.
06-07-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35809612

Rabies is a zoonotic viral disease with inevitably fatal outcome. Toll-like receptor 3 (TLR3) could sense dsRNA viral infections, and implicated in pathogenesis of rabies and Negri bodies (NBs) formation. Present study was undertaken to elucidate the role of TLR3 in pathogenesis, NBs formation, and therapeutic potential of blocking TLR3/dsRNA interaction in rabies infection. Young Swiss albino mice were infected with 100 LD_{50} of street rabies virus (SRABV) intracerebrally (i/c) on day 0 and treated with 30 µg of CU CPT 4a (selective TLR3 inhibitor) i/c on 0, 3 and 5 days post-infection (DPI). Three mice each were sacrificed at 1, 3, 5, 7, 9, 11, and 13 DPI to study sequential pathological consequences through histopathology, Seller's staining, immunofluorescence, immunohistochemistry, TUNEL assay, flow cytometry, and viral and cytokine genes quantification by real-time PCR. CU CPT 4a inhibited TLR3 expression resulted in delayed development and decreased intensity of clinical signs and pathological lesions, low viral load, significantly reduced NBs formation, and increased survival time in SRABV-infected mice. These parameters suggested that TLR3 did influence the SRABV replication and NBs formation. Inhibition of TLR3 led to decreased expression of pro-inflammatory cytokines and interferons indicated an anti-inflammatory effect of CU CPT 4a during SRABV infection. Further, TLR3-inhibited group revealed normal $CD4^+/CD8^+$ T-cells ratio with less TUNEL-positive apoptotic cells indicated that immune cell kinetics are not affected during TLR3-inhibition. SRABV-infected and mock-treated mice were developed severe clinical signs and histopathological lesions, more NBs formation, high viral load, increased pro-inflammatory cytokines expression in brain, which were correlated with higher expression levels of TLR3. In conclusion, these data suggested that TLR3/dsRNA signaling pathway could play critical role in pathogenesis of SRABV infection in vivo and opens up new avenues of therapeutics.

Heterogeneity in dog population characteristics contributes to chronic under-vaccination against rabies in Guatemala.

Moran, D., Alvarez, D., Cadena, L., Cleaton, J., Salyer, S., Pieracci, E., Camposeco, L., Bernal, S., Wallace, R.
07-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010522

Guatemala has held dog rabies mass vaccination campaigns countrywide since 1984, yet the virus remains endemic. To eliminate dog-mediated human rabies, dog vaccination coverage must reach at least 70%. The Guatemala rabies program uses a 5:1 human:dog ratio (HDR) to estimate the vaccination coverage; however, this method may not accurately reflect the heterogeneity of dog ownership practices in Guatemalan communities. We conducted 16 field-based dog population estimates in urban, semi-urban and rural areas of Guatemala to determine HDR and evaluate the

standard 5:1. Our study-derived HDR estimates varied from 1.7-11.4:1 (average 4.0:1), being higher in densely populated sites and lowest in rural communities. The community-to-community heterogeneity observed in dog populations could explain the persistence of rabies in certain communities. To date, this is the most extensive dog-population evaluation conducted in Guatemala, and can be used to inform future rabies vaccination campaigns needed to meet the global 2030 rabies elimination targets.

Public health risks for relaxing quarantine for pet dogs entering with Ukrainian refugees.

Kaneda, Y., Sakeshima, K., Takahashi, K., Ozaki, A., Tanimoto, T.
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QJM
https://doi.org/10.1093/qjmed/hcac135

TRACHOME

Historical overview and geographical distribution of neglected tropical diseases amenable to preventive chemotherapy in the Republic of the Congo: A systematic review.

Ngatse, J., Ndziessi, G., Missamou, F., Kinouani, R., Hemilembolo, M., Pion, S., Bork, K., Abena, A., Boussinesq, M., Chesnais, C.
11-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010560

Background: Neglected Tropical Diseases amenable to Preventive Chemotherapy (PC-NTDs) affect the poorest populations around the world, especially in Africa. Scientific information on the distribution and level of endemicity of these diseases in the Republic of the Congo (RoC) is scarce in the published literature. We sought to collect all available epidemiological data on PC-NTDs in the RoC to document the historical and current situation and identify challenges in reaching the elimination of NTDs. Methods: We searched Medline and Horizon databases for studies published until to July 4th, 2019, on onchocerciasis, lymphatic filariasis, soil-transmitted helminth infections, schistosomiasis, and trachoma in the RoC. Unpublished reports were also reviewed. We included all epidemiological studies containing community data and excluded case reports. Location, prevalence data, and dates of the studies were extracted. Principal findings: We identified 933 records, of which 56 met the inclusion criteria. The articles published before 1960 mainly concerned onchocerciasis and schistosomiasis. Despite a low number over the studied period, since 2005 there has been a steady increase in the number of publications. Most of the studies were cross-sectional and conducted in the general population. Trachoma is endemic in the Sangha and Likouala departments (prevalence of trachomatous inflammation-follicular > 5% in some villages), and further mapping is essential to properly assess the burden of this disease in the country. While the prevalence of soil-transmitted helminths is still high (over 20%) in a large part of Congo, cases of lymphatic filariasis (based on Wuchereria bancrofti antigenaemia and/or microfilaraemia) and onchocerciasis are becoming rare and very focused. To achieve the elimination of PC-NTDs, further intervention is required. Conclusions: Except for trachoma, whose epidemiological situation should be better evaluated, PC-NTDs are endemic in the RoC, and actions to control them have been taken by health authorities. To eliminate PC-NTDs, which are still present in some locations, new mapping surveys are needed, and increased investment in scientific research should be encouraged in the country.

Forecasting the elimination of active trachoma: An empirical model.

Renneker, K., Emerson, P., Hooper, P., Ngondi, J.
11-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010563

Background: Great progress has been made toward the elimination of trachoma as a public-health problem. Mathematical and statistical models have been used to forecast when the program will attain the goal of the elimination of active trachoma, defined as prevalence of trachomatous inflammation-follicular in 1-9 year olds (TF1-9) <5%. Here we use program data to create an empirical model predicting the year of attaining global elimination of TF1-9. Methodology/Principal findings: We calculated the mean number of years (95% CI) observed for an implementation unit (IU) to move from a baseline TF1-9 prevalence ≥5% to the elimination threshold, based on the region (Ethiopia vs. non-Ethiopia) and baseline prevalence category. Ethiopia IUs had significantly different rates of reaching the TF1-9 elimination threshold after a trachoma impact survey (TIS) compared to non-Ethiopia IUs across all baseline categories. We used those estimates to predict when remaining active trachoma-endemic IUs (TF1-9 ≥5%) would have their last round of mass drug administration (MDA) based on the mean number of years required and number of MDA rounds already completed. Our model predicts that elimination of TF1-9 will be achieved in 2028 in Ethiopia (95% CI: 2026-2033) and 2029 outside of Ethiopia (95% CI: 2023-2034), with some IUs in East Africa predicted to be the last requiring MDA globally. Conclusions/Significance: Our empirical estimate is similar to those resulting from previous susceptible-infectious-susceptible (SIS) and mathematical models, suggesting that the forecast achievement of TF1-9 elimination is realistic with the caveat that although disease elimination progress can be predicted for most IUs, there is an important minority of IUs that is not declining or has not yet started trachoma elimination activities. These IUs represent an important barrier to the timely global elimination of active trachoma.

Bortezomib Eliminates Persistent *Chlamydia trachomatis* Infection through Rapid and Specific Host Cell Apoptosis.

Itoh, R., Kurihara, Y., Yoshimura, M., Hiromatsu, K.
04-07-2022
Int J Mol Sci
https://pubmed.ncbi.nlm.nih.gov/35806436

Chlamydia trachomatis, a parasitic intracellular bacterium, is a major human pathogen that causes millions of trachoma, sexually transmitted infections, and pneumonia cases worldwide. Previously, peptidomimetic inhibitors consisting of a hydrophobic dipeptide derivative exhibited significant inhibitory effects against chlamydial growth. Based on this finding, this study showed that both bortezomib (BTZ) and ixazomib (IXA), anticancer drugs characterized by proteasome inhibitors, have intensive inhibitory activity against *Chlamydia*. Both BTZ and IXA consisted of hydrophobic dipeptide derivatives and strongly restricted the growth of *Chlamydia* (BTZ, IC_{50} = 24 nM). In contrast, no growth inhibitory effect was observed for other nonintracellular parasitic bacteria, such as *Escherichia coli*. BTZ and IXA appeared to inhibit chlamydial growth bacteriostatically via electron microscopy. Surprisingly, *Chlamydia*-infected cells that induced a persistent infection state were selectively eliminated by BTZ treatment, whereas uninfected cells survived. These results strongly suggested the potential of boron compounds based on hydrophobic dipeptides for treating chlamydial infections, including persistent infections, which may be useful for future therapeutic use in chlamydial infectious diseases.

ULCERE DE BURULI

Comparison of 8 weeks standard treatment (rifampicin plus clarithromycin) vs. 4 weeks standard plus amoxicillin/clavulanate treatment [RC8 vs. RCA4] to shorten Buruli ulcer disease therapy (the BLMs4BU trial): study protocol for a randomized controlled multi-centre trial in Benin.

Johnson, R., Sáez-López, E., Anagonou, E., Kpoton, G., Ayelo, A., Gnimavo, R., Mignanwande, F., Houezo, J., Sopoh, G., Addo, J., Orford, L., Vlasakakis, G., Biswas, N., Calderon, F., Della Pasqua, O., Gine-March, A., Herrador, Z., Mendoza-Losana, A., Díez, G., Cruz, I., Ramón-García, S.
08-07-2022
Trials
https://doi.org/10.1186/s13063-022-06473-9

Background: Buruli ulcer (BU) is a neglected tropical disease caused by Mycobacterium ulcerans that affects skin, soft tissues, and bones, causing long-term morbidity, stigma, and disability. The recommended treatment for BU requires 8 weeks of daily rifampicin and clarithromycin together with wound care, physiotherapy, and sometimes tissue grafting and surgery. Recovery can take up to 1 year, and it may pose an unbearable financial burden to the household. Recent in vitro studies demonstrated that beta-lactams combined with rifampicin and clarithromycin are synergistic against M. ulcerans. Consequently, inclusion of amoxicillin/clavulanate in a triple oral therapy may potentially improve and shorten the healing process. The BLMs4BU trial aims to assess whether co-administration of amoxicillin/clavulanate with rifampicin and clarithromycin could reduce BU treatment from 8 to 4 weeks. Methods: We propose a randomized, controlled, open-label, parallel-group, non-inferiority phase II, multi-centre trial in Benin with participants stratified according to BU category lesions and randomized to two oral regimens: (i) Standard: rifampicin plus clarithromycin therapy for 8 weeks; and (ii) Investigational: standard plus amoxicillin/clavulanate for 4 weeks. The primary efficacy outcome will be lesion healing without recurrence and without excision surgery 12 months after start of treatment (i.e. cure rate). Seventy clinically diagnosed BU patients will be recruited per arm. Patients will be followed up over 12 months and managed according to standard clinical care procedures. Decision for excision surgery will be delayed to 14 weeks after start of treatment. Two sub-studies will also be performed: a pharmacokinetic and a microbiology study. Discussion: If successful, this study will create a new paradigm for BU treatment, which could inform World Health Organization policy and practice. A shortened, highly effective, all-oral regimen will improve care of BU patients and will lead to a decrease in hospitalization-related expenses and indirect and social costs and improve treatment adherence. This trial may also provide information on treatment shortening strategies for other mycobacterial infections (tuberculosis, leprosy, or non-tuberculous mycobacteria infections). ClinicalTrials.gov NCT05169554 . Registered on 27 December 2021.

PIAN

Stigma, psychosocial and economic effects of yaws in the Philippines: an exploratory, qualitative study.

Dofitas, B., Kalim, S., Toledo, C., Richardus, J.
06-07-2022
Trop Med Health
https://doi.org/10.1186/s41182-022-00433-4

Background: Yaws is a chronic, non-venereal, highly contagious skin and bone infection affecting children living in impoverished, remote communities and caused by Treponema pallidum subspecie pertenue. Social stigma and economic losses due to yaws have been reported anecdotally in the Southern Philippines but have not been well-documented. Objective: To describe and compare the psychological, social, and economic effects of yaws from the perspective of patients, contacts, and key informants in two areas of the Philippines. Materials and methods: Yaws and contacts were identified through clinicoseroprevalence surveys conducted in

the Liguasan Marsh area, Mindanao, Southern Philippines in 2017 and among the Aetas, an indigenous people community in Quezon province, Luzon region in 2020. Skin examinations and serologic tests confirmed the diagnosis of active, latent, or past yaws among the children and adults. Trained health personnel conducted in-depth interviews of those affected by yaws and their guardians, household contacts, and key informants, such as health workers regarding their perceptions, feelings, health-seeking behaviors, and effects of yaws on their lives. **Results:** A total of 26 participants were interviewed: 17 from Mindanao and 9 from Luzon. Aside from the physical discomforts and embarrassment, yaws was considered stigmatizing in Mindanao, because positive non-treponemal tests or treponemal antibody tests were associated with syphilis and promiscuity. These have led to loss of employment and income opportunities for adults with latent or past yaws. In contrast, the Aetas of Luzon did not perceive yaws as stigmatizing, because it was a common skin problem. Plantar yaws interfered with the Aeta's gold panning livelihood due to the pain of wounds. **Conclusions:** Yaws is not merely a chronic skin and bone disease. It can lead to significant psychosocial and economic problems as well. Yaws is a generally forgotten disease in the Philippines. There is no yaws surveillance and control program. Treatments are not readily available for the populations affected, thus perpetuating the infection and negative effects. **Significance of study:** This is the first study to document the psychosocial and economic effects of yaws among Filipinos. Information campaigns about yaws and a yaws control program are needed to reduce stigma and discrimination.

A simple, high-throughput and validated LC-MS/MS method for determination of azithromycin in human plasma and its application to a clinical pharmacokinetic study.

Zhang, Y., Bala, V., Chhonker, Y., Aldhafiri, W., John, L., Bjerum, C., King, C., Mitja, O., Marks, M., Murry, D.
05-07-2022
Biomed Chromatogr
https://doi.org/10.1002/bmc.5443

A sensitive, specific and rapid liquid chromatographic-tandem mass spectrometric (LC-MS/MS) method was developed and validated to quantify azithromycin concentrations in human plasma. Azithromycin (AZI) is the most common outpatient prescribed antibiotic in the US and clinical studies have demonstrated the efficacy and safety of AZI in many bacterial infections. To support a clinical study, we developed a high throughput LC-MS/MS method to process up to 250 samples per day to quantify AZI in human plasma. Samples were prepared by solid phase extraction. Separation was achieved with an ACE C_{18} column (2.1 x 100 mm, 1.7 µm) equipped with a C_{18} guard column. The mobile phase consisted of 0.1% formic acid and methanol/acetonitrile (1:1, v/v) at a flow rate of 0.25 mL/min. The ionization was optimized with positive electrospray source using multiple reaction monitoring transition, m/z 749.50>591.45 for AZI and m/z 754.50>596.45 for AZI-d5. Extraction recoveries were approximately 90% for AZI. The assay was linear from 0.5 to 2000 ng/mL and required only 100 µL of plasma with total analysis time of 4.5 minutes. The method was successfully applied to pharmacokinetic studies of a weight-based dosing protocol for AZI.

LEPRE

Leprosy: A Review of Epidemiology, Clinical Diagnosis, and Management.

Revue de littérature

Chen, K., Lin, C., Su, S., Chen, K.
04-07-2022
J Trop Med
https://doi.org/10.1155/2022/8652062

Leprosy is a neglected infectious disease caused by acid-fast bacillus *Mycobacterium leprae*. It primarily affects the skin and then progresses to a secondary stage, causing peripheral neuropathy with potential long-term disability along with stigma. Leprosy patients account for a significant proportion of the global disease burden. Previous efforts to improve diagnostic and therapeutic techniques have focused on leprosy in adults, whereas childhood leprosy has been relatively neglected. This review aims to update the diagnostic and therapeutic recommendations for adult and childhood leprosy. This review summarizes the clinical, bacteriological, and immunological approaches used in the diagnosis of leprosy. As strategies for the diagnosis and management of leprosy continue to develop better and more advanced knowledge, control and prevention of leprosy are crucial.

An evidence and reasoning based differential diagnosis of a case of leprosy reinfection from reaction and relapse.

Kumar, V., Arora, M., Gupta, V., Singh, A., Patil, S.
09-07-2022
Indian J Med Microbiol
https://pubmed.ncbi.nlm.nih.gov/35820982

Leprosy is caused by Mycobacterium leprae (M. leprae) and is unique in terms of the chronicity of the disease and its prolonged treatment protocol. Even after the introduction of multidrug therapy (MDT) by World health organization (WHO), large numbers of new cases (nearly 200,000) of leprosy are reported yearly, indicating active transmission, especially in developing countries. Recurrent clinical manifestations after MDT can occur due to leprosy reactions, relapse or reinfection. It is very difficult to differentiate reaction, relapse and reinfection. Here we categorized a recent case of reoccurrence of leprosy as reinfection by differentiating it from reaction and relapse based on evidence and by analysing the clinical data of the patient.

Comparison of 8 weeks standard treatment (rifampicin plus clarithromycin) vs. 4 weeks standard plus amoxicillin/clavulanate treatment [RC8 vs. RCA4] to shorten Buruli ulcer disease therapy (the BLMs4BU trial): study protocol for a randomized controlled multi-centre trial in Benin.

Johnson, R., Sáez-López, E., Anagonou, E., Kpoton, G., Ayelo, A., Gnimavo, R., Mignanwande, F., Houezo, J., Sopoh, G., Addo, J., Orford, L., Vlasakakis, G., Biswas, N., Calderon, F., Della Pasqua, O., Gine-March, A., Herrador, Z., Mendoza-Losana, A., Díez, G., Cruz, I., Ramón-García, S.
08-07-2022
Trials
https://doi.org/10.1186/s13063-022-06473-9

Background: Buruli ulcer (BU) is a neglected tropical disease caused by Mycobacterium ulcerans that affects skin, soft tissues, and bones, causing long-term morbidity, stigma, and disability. The recommended treatment for BU requires 8 weeks of daily rifampicin and clarithromycin together with wound care, physiotherapy, and sometimes tissue grafting and surgery. Recovery can take up to 1 year, and it may pose an unbearable financial burden to the household. Recent in vitro studies demonstrated that beta-lactams combined with rifampicin and clarithromycin are synergistic against M. ulcerans. Consequently, inclusion of amoxicillin/clavulanate in a triple oral therapy may potentially improve and shorten the healing process. The BLMs4BU trial aims to assess whether co-administration of amoxicillin/clavulanate with rifampicin and clarithromycin could reduce BU treatment from 8 to 4 weeks. Methods: We propose a randomized, controlled, open-label, parallel-group, non-inferiority phase II, multi-centre trial in Benin with participants stratified according to BU category lesions and randomized to two oral regimens: (i) Standard: rifampicin plus clarithromycin therapy for 8 weeks; and (ii) Investigational: standard plus amoxicillin/clavulanate for 4 weeks. The primary efficacy outcome will be lesion healing without recurrence and without excision surgery 12 months after start of treatment (i.e. cure rate). Seventy clinically diagnosed BU patients will be recruited per arm. Patients will be followed up over 12 months and managed according to standard clinical care procedures. Decision for excision surgery will be delayed to 14 weeks after start of treatment. Two sub-studies will also be performed: a pharmacokinetic and a microbiology study. Discussion: If successful, this study will create a new paradigm for BU treatment, which could inform World Health Organization policy and practice. A shortened, highly effective, all-oral regimen will improve care of BU patients and will lead to a decrease in hospitalization-related expenses and indirect and social costs and improve treatment adherence. This trial may also provide information on treatment shortening strategies for other mycobacterial infections (tuberculosis, leprosy, or non-tuberculous mycobacteria infections). ClinicalTrials.gov NCT05169554 . Registered on 27 December 2021.

MiR-1290: a potential therapeutic target for regenerative medicine or diagnosis and treatment of non-malignant diseases.

Revue de littérature

Kalhori, M., Soleimani, M., Yari, K., Moradi, M., Kalhori, A.
08-07-2022
Clin Exp Med
https://doi.org/10.1007/s10238-022-00854-9

MicroRNAs are a set of small non-coding RNAs that could change gene expression with post-transcriptional regulation. MiRNAs have a significant role in regulating molecular signaling pathways and innate and adaptive immune system activity. Moreover, miRNAs can be utilized as a powerful instrument for tissue engineers and regenerative medicine by altering the expression of genes and growth factors. MiR-1290, which was first discovered in human embryonic stem cells, is one of those miRNAs that play an essential role in developing the fetal nervous system. This review aims to discuss current findings on miR-1290 in different human pathologies and determine whether manipulation of miR-1290 could be considered a possible therapeutic strategy to treat different non-malignant diseases. The results of these studies suggest that the regulation of miR-1290 may be helpful in the treatment of some bacterial (leprosy) and viral infections (HIV, influenza A, and Borna disease virus). Also, adjusting the expression of miR-1290 in non-infectious diseases such as celiac disease, necrotizing enterocolitis, polycystic ovary syndrome, pulmonary fibrosis, ankylosing spondylitis, muscle atrophy, sarcopenia, and ischemic heart disease can help to treat these diseases better. In addition to acting as a biomarker for the diagnosis of non-malignant diseases (such as NAFLD, fetal growth, preeclampsia, down syndrome, chronic rhinosinusitis, and oral lichen planus), the miR-1290 can also be used as a valuable instrument in tissue engineering and reconstructive medicine. Consequently, it is suggested that the regulation of miR-1290 could be considered a possible therapeutic target in the treatment of non-malignant diseases in the future.

Multibacillary leprosy with an incubation period exceeding 50 years.

Taggart, M., Kelly, A., Stell, R., Chu, E.
05-07-2022
BMJ Case Rep
https://pubmed.ncbi.nlm.nih.gov/35790324

Leprosy is a chronic granulomatous infection predominantly involving the skin and peripheral nervous system. The condition is caused by infection with the obligate intracellular bacillus *Mycobacterium leprae* and the clinical phenotype is largely dependent on the host immune response to the organism. Transmission is suspected to occur via respiratory secretions with infection usually requiring prolonged periods of contact. The incubation period is highly variable with disease manifestations appearing up to several decades after the initial exposure. The disease can be broadly divided into 'paucibacillary' and 'multibacillary', and treatment with multidrug therapy including dapsone, clofazimine and

rifampicin offers high rates of cure. Here, we report of a case of leprosy with a suspected incubation period in excess of 50 years following occupational exposure in rural 17Australia. To our knowledge, this incubation period is the longest reported to date.

TRYPANOSOMES (TRYPANOSOMIASE ET MALADIE DE CHAGAS)

Subregional initiatives for Chagas disease. A path of technical cooperation, opened by the countries, as an approach to a neglected disease.

Lima, J.
06-07-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35830011

Chagas disease control-surveillance in the Americas: the multinational initiatives and the practical impossibility of interrupting vector-borne Trypanosoma cruzi transmission.

de Arias, A., Monroy, C., Guhl, F., Sosa-Estani, S., Santos, W., Abad-Franch, F.
06-07-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35830010

Chagas disease (CD) still imposes a heavy burden on most Latin American countries. Vector-borne and mother-to-child transmission cause several thousand new infections per year, and at least 5 million people carry Trypanosoma cruzi. Access to diagnosis and medical care, however, is far from universal. Starting in the 1990s, CD-endemic countries and the Pan American Health Organization-World Health Organization (PAHO-WHO) launched a series of multinational initiatives for CD control-surveillance. An overview of the initiatives' aims, achievements, and challenges reveals some key common themes that we discuss here in the context of the WHO 2030 goals for CD. Transmission of T. cruzi via blood transfusion and organ transplantation is effectively under control. T. cruzi, however, is a zoonotic pathogen with 100+ vector species widely spread across the Americas; interrupting vector-borne transmission seems therefore unfeasible. Stronger surveillance systems are, and will continue to be, needed to monitor and control CD. Prevention of vertical transmission demands boosting current efforts to screen pregnant and childbearing-aged women. Finally, integral patient care is a critical unmet need in most countries. The decades-long experience of the initiatives, in sum, hints at the practical impossibility of interrupting vector-borne T. cruzi transmission in the Americas. The concept of disease control seems to provide a more realistic description of what can in effect be achieved by 2030.

Chagas disease and mobility: comments on the challenges for access and the right to health for migrants.

Peiter, P.
08-07-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35830005

Population movements, borders, and Chagas disease.

Avaria, A., Ventura-Garcia, L., Sanmartino, M., Van der Laat, C.
08-07-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35830004

Currently, Chagas disease is a complex global health problem with local and global implications. In the present article, we approach this complexity from the perspective of human mobility and its effects on people's health in places of origin and in transit and destination. We raise key concepts such as human mobility - understood as a possible socio-structural and economic determination of health -, the associated social and institutional barriers and the processes of social exclusion related to Chagas disease. We also propose what we identify as emerging opportunities from the perspective of health as a right. Finally, we propose strategies aimed at addressing Chagas disease from a multidimensional and intersectional perspective in complex, diverse and interconnected territories through migration.

Traditional use of benznidazole with weekly clinical follow-up indicate to be an important approach for the etiologic treatment of Chagas disease.

Sperandio da Silva, G.
08-07-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35830003

Critical analysis of Chagas disease treatment in different countries.

Revue de littérature

Mendes, F., Perez-Molina, J., Angheben, A., Meymandi, S., Sosa-Estani, S., Molina, I.
08-07-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35830002

As a result of globalization and constant migratory flows, Chagas disease is now present in almost all continents. The management and treatment of the disease is often influenced by the economic and social context of the societies that host patients. In this manuscript, we aim to provide a comparative review of approaches to patients with Chagas disease in the Americas and Europe.

Improving the oral delivery of benznidazole nanoparticles by optimizing the formulation parameters through a design of experiment and optimization strategy.

Arrua, E., Hartwig, O., Loretz, B., Goicoechea, H., Murgia, X., Lehr, C., Salomon, C.
07-07-2022
Colloids Surf B Biointerfaces
https://pubmed.ncbi.nlm.nih.gov/35816885

Chagas disease is a neglected tropical disease affecting the American continent and also some regions of Europe. Benznidazole, approved by FDA, is a drug of choice but its poor aqueous solubility may lead to a low bioavailability and efficacy. Therefore, the aim of this study was to formulate nanoparticles of benznidazole for improving its solubility, dissolution and permeability. A Plackett-Burman design was applied to identify the effect of 5 factors over 4 responses. Then, a Central Composite design was applied to estimate the values of the most important factors leading to the best compromise between highest nanoprecipitation efficiency, drug solubility and lower particle size. The optimized nanoparticles were evaluated for in vitro drug release in biorelevant media, stability studies and transmission electron microscopy. Biocompatibility and permeability of nanoparticles were evaluated on the Caco-2 cell line. The findings of the optimization process indicated that concentration of drug and stabilizer influenced significantly the particle size while concentration of stabilizer and organic/water phase volume ratio mainly influenced the drug solubility. Stability studies suggested that benznidazole nanoparticles were stable after 12 months at different temperatures. Minimal interactions of those nanoparticles and mucin glycoproteins suggested favorable properties to address the intestinal mucus barrier. Cell viability studies confirmed the safety profile of the optimized formulation and showed an increased permeation through the Caco-2 cells. Thus, this study confirmed the suitability of the design of experiment and optimization approach to elucidate critical parameters influencing the quality of benznidazole nanoparticles, which could lead to a more efficient management of Chagas disease by oral route.

Estimating the genetic structure of Triatoma dimidiata (Hemiptera: Reduviidae) and the transmission dynamics of Trypanosoma cruzi in Boyacá, eastern Colombia.

Velásquez-Ortiz, N., Hernández, C., Cantillo-Barraza, O., Medina, M., Medina-Alfonso, M., Suescún-Carrero, S., Muñoz, M., Vega, L., Castañeda, S., Cruz-Saavedra, L., Ballesteros, N., Ramírez, J.
11-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010534

Chagas disease is considered a public health issue in Colombia, where many regions are endemic. Triatoma dimidiata is an important vector after Rhodnius prolixus, and it is gaining importance in Boyacá, eastern Colombia. Following the recent elimination of R. prolixus in the region, it is pivotal to understand the behavior of T. dimidiata and the transmission dynamics of T. cruzi. We used qPCR and Next Generation Sequencing (NGS) to evaluate T. cruzi infection, parasite load, feeding profiles, and T. cruzi genotyping for T. dimidiata specimens collected in nine municipalities in Boyacá and explored T. dimidiata population genetics. We found that T. dimidiata populations are composed by a single population with similar genetic characteristics that present infection rates up to 70%, high parasite loads up to 1.46 × 109 parasite-equivalents/mL, a feeding behavior that comprises at least 17 domestic, synanthropic and sylvatic species, and a wide diversity of TcI genotypes even within a single specimen. These results imply that T. dimidiata behavior is similar to other successful vectors, having a wide variety of blood sources and contributing to the circulation of different genotypes of the parasite, highlighting its importance for T. cruzi transmission and risk for humans. In the light of the elimination of R. prolixus in Boyacá and the results we found, we suggest that T. dimidiata should become a new target for vector control programs. We hope this study provides enough information to enhance surveillance programs and a future effective interruption of T. cruzi vector transmission in endemic regions.

Modelling to infer the role of animals in gambiense human African trypanosomiasis transmission and elimination in the DRC.

Crump, R., Huang, C., Spencer, S., Brown, P., Shampa, C., Mwamba Miaka, E., Rock, K.
11-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010599

Gambiense human African trypanosomiasis (gHAT) has been targeted for elimination of transmission (EoT) to humans by 2030. Whilst this ambitious goal is rapidly approaching, there remain fundamental questions about the presence of non-human animal transmission cycles and their potential role in slowing progress towards, or even preventing, EoT. In this study we focus on the country with the most gHAT disease burden, the Democratic Republic of Congo (DRC), and use mathematical modelling to assess whether animals may contribute to transmission in specific regions, and if so, how their presence could impact the likelihood and timing of EoT. By fitting two model variants-one with, and one without animal transmission-to the human case data from 2000-2016 we estimate model parameters for 158 endemic health zones of the DRC. We evaluate the statistical support for each model variant in each health zone and infer the contribution of animals to overall transmission and how this could impact predicted time to EoT. We conclude that there are 24/158 health zones where there is substantial to decisive statistical support for some animal transmission. However-even in these regions-we estimate that animals would be extremely unlikely to maintain transmission on their own. Animal transmission could hamper progress towards EoT in some settings, with

projections under continuing interventions indicating that the number of health zones expected to achieve EoT by 2030 reduces from 68/158 to 61/158 if animal transmission is included in the model. With supplementary vector control (at a modest 60% tsetse reduction) added to medical screening and treatment interventions, the predicted number of health zones meeting the goal increases to 147/158 for the model including animal transmission. This is due to the impact of vector reduction on transmission to and from all hosts.

Imidazole and nitroimidazole derivatives as NADH-fumarate reductase inhibitors: Density functional theory studies, homology modeling, and molecular docking.

Campos-Fernández, L., Ortiz-Muñiz, R., Cortés-Barberena, E., Mares-Sámano, S., Garduño-Juárez, R., Soriano-Correa, C.
07-07-2022
J Comput Chem
https://doi.org/10.1002/jcc.26959

Chagas disease is caused by Trypanosoma cruzi. Benznidazole and nifurtimox are drugs used for its therapy; nevertheless, they have collateral effects. NADH-fumarate (FUM) reductase is a potential pharmacological target since it is essential for survival of parasite and is not found in humans. The objectives are to design and characterize the electronic structure of imidazole and nitroimidazole derivatives at DFT-M06-2X level in aqueous solution; also, to model the NADH-FUM reductase and analyze its intermolecular interactions by molecular docking. Quantum-chemical descriptors allowed to select the molecules with the best physicochemical properties and lowest toxicity. A high-quality three-dimensional structure of NADH-FUM reductase was obtained by homology modeling. Water molecules do not have influence in the interaction between FUM and NADH-FUM reductase. The main hydrogen-binding interactions for FUM were identified in NADH, Lys172, and Arg89; while hydrophobic interactions in Phe479, Thr174, Met63. The molecules S3-8, S2-8, and S1-8 could be inhibitors of NADH-FUM reductase.

Tropical Parasitic Itch in Returned Travelers and Immigrants from Endemic Areas.

Revue de littérature

Ju, T., Vander Does, A., Ingrasci, G., Norton, S., Yosipovitch, G.
06-07-2022
J Eur Acad Dermatol Venereol
https://doi.org/10.1111/jdv.18408

Itch is the most common skin symptom among tropical parasitic diseases (TPD) but there are limited data about its characteristics in these conditions. In dermatology practices and travelers' health clinics in the developed world, itch is a common complaint among travelers returning from endemic areas, as well among migrants arriving from endemic areas, where they may have been exposed to TPD. Studying aspects of pruritus among TPD may lead to improvements in prompt, accurate diagnosis and management of these conditions. This review examines the major itch-inducing TPDs, including schistosomiasis, echinococcosis, onchocerciasis, scabies, cutaneous larva migrans, larva currens, African trypanosomiasis, dracunculiasis, and other causes of travel associated pruritus. We focus on the link between pruritus and other symptoms, etiology, clinical staging, and therapy options for these parasitic illnesses. Because some tropical parasitic diseases can present with significant pruritus, we attempt to identify aspects of the pruritus that are characteristic of-or unique to-specific conditions. These diagnostic insights may help clinicians create a rational and focused differential diagnosis and help determine optimal disease management pathways. In this sense, management involves treating the individual, seeking epidemiologically linked cases, preventing recurrences or relapses, and reducing spread of the disease.

Geospatial analysis as a tool to identify target areas for Chagas disease education for healthcare providers.

Pacheco, G., Fulton, L., Betancourt, J., Shanmugam, R., Granados, P.
04-07-2022
BMC Infect Dis
https://doi.org/10.1186/s12879-022-07577-y

Chagas Disease (CD) is a neglected zoonotic disease of the Americas. It can be fatal if not diagnosed and treated in its early stages. Using geospatial and sensitivity analysis, this study focuses on understanding how to better allocate resources and educational information to areas in the United States, specifically Texas, that have the potential for increased risk of CD cases and the associated costs of addressing the disease. ICD-9 and 10 inpatient hospital diagnostic codes were used to illustrate the salience of potentially missed CD diagnoses (e.g., cardiomyopathic diagnoses) and where these are occurring with more frequency. Coding software along with GIS and Microsoft Excel 3D mapping were used to generate maps to illustrate where there may be a need for increased statewide surveillance and screening of populations at greater risk for CD. The CD cases reported to the Texas Department of State Healthcare Services (TxDSHS) are not homogenously dispersed throughout the state but rather, reveal that the incidences are in clusters and primarily in urban areas, where there is increased access to physician care, CD research and diagnostic capabilities.

Preclinical advances and the immunophysiology of a new therapeutic Chagas disease vaccine.

Jones, K., Poveda, C., Versteeg, L., Bottazzi, M., Hotez, P.
04-07-2022
Expert Rev Vaccines
https://doi.org/10.1080/14760584.2022.2093721

Introduction: Chronic infection with the protozoal parasite *Trypanosoma cruzi* leads to a progressive cardiac disease, known as chronic Chagasic cardiomyopathy (CCC). A new

therapeutic Chagas disease vaccine is in development to augment the existing antiparasitic chemotherapy drugs. **Areas Covered:** We report on our current understanding of the underlying immunologic and physiologic mechanisms that lead to CCC, including parasite immune escape mechanisms that allow persistence and the subsequent inflammatory and fibrotic processes that lead to clinical disease. We report on vaccine design and the observed immunotherapeutic effects including induction of a balanced $T_H1/T_H2/T_H17$ immune response that leads to reduced parasite burdens and tissue pathology. Furthermore, we report vaccine-linked chemotherapy, a dose-sparing strategy to further reduce parasite burdens and tissue pathology. **Expert Opinion:** Our vaccine-linked chemotherapeutic approach is a multimodal treatment strategy, addressing both the parasite persistence and the underlying deleterious host inflammatory and fibrotic responses that lead to cardiac dysfunction. In targeting treatment towards patients with chronic indeterminate or early determinate Chagas disease, this vaccine-linked chemotherapeutic approach will be highly economical and will reduce the global disease burden and deaths due to CCC.

LEISHMANIOSE

Combined immunotherapeutic effect of Leishmania-derived recombinant aldolase and Ambisome against experimental visceral leishmaniasis.

Keerti, ., Yadav, N., Joshi, S., Ratnapriya, S., Sahasrabuddhe, A., Dube, A.
04-07-2022
J Microbiol Immunol Infect
https://pubmed.ncbi.nlm.nih.gov/35835687

Background: Available therapeutics for visceral leishmaniasis (VL), a deadly parasitic infection, are usually associated with inadequate efficacy and adverse aftereffects. Further, the primary site of Leishmania parasite are host macrophages resulting in compromised immunity; ensuing marked T-cell immunosuppression. Such settings emphasize the exploration of chemo-immunotherapeutic strategies for improvising the infected person's immune status with better resolution of infection. **Methods:** Present work employs the immunization of Leishmania-infected hamsters with Leishmania-derived recombinant aldolase (rLdAld) and enolase (rLdEno) proteins in consort with the sub-optimal dose of Ambisome (2.5 mg/kg). After the completion of immunization, hamsters were sacrificed on day 60 and 90 post infection and different organ samples were collected to perform immunological assay for evaluating the therapeutic efficacy and modulation in protective cellular immune responses. **Results:** Combining these proteins, particularly rLdAld with Ambisome (2.5 mg/kg), has significantly reduced the parasitic load (~80%) with remarkable enhancement in DTH and lymphoproliferative responses compared to the infected control and only Ambisome treated groups. Moreover, cytokine levels at RNA and protein levels were noticed to be inclined towards Th-1 phenotype through up-regulation of IFN-γ and TNF-α with significant down-regulation in IL-10 and TGF-β expression, an indication towards the generation of protective immunity against experimental VL. **Conclusion:** Our experimental findings demonstrated that the chemo-immunotherapeutic approach could be an effective way of controlling human VL infection at minimal dosages of antileishmanial with reduced side-effects and propensity of drug resistance emergence.

Pharmacokinetics, biodistribution, and activity of Amphotericin B-loaded nanocochleateson the Leishmania donovanimurine visceral leishmaniasis model.

Lipa Castro, A., Pomel, S., Cailleau, C., Fournier, N., Dennemont, I., Loiseau, P., Barratt, G.
09-07-2022
Int J Pharm
https://pubmed.ncbi.nlm.nih.gov/35820519

Amphotericin B (AmB) is an effective drug to treat visceral leishmaniasis but its use is limited by its poor oral bioavailability. This article describes the in-vivo evaluation of AmB-loaded, lipid-based cochleate systems designed for the oral route. Two different cochleate formulations were studied: one based on the synthetic phospholipid dioleoylphosphatidylserine (DOPS) and another optimized formulation based on a naturally occurring phosphatidylserine (Lipoid PSP70) that would render the formulation more affordable in developing countries. Their antiparasitic activity was evaluated in a mouse model of visceral leishmaniasis. Limited efficacy was observed for the DOPS-based cochleates after three doses of AmB at 1 mg/kg. The Lipoid PSP70-based cochleates were administered either as a buffered suspension or in enteric-coated capsules. AmB-loaded cochleates administered as a suspension at a high dose (3 x 20mg/kg) exhibited significant antiparasitic activity while AmB-loaded cochleates in enteric-coated capsules at a lower dose (3 x 5mg/kg) presented a slightly higher significant activity. A pharmacokinetic and biodistribution study in rats was performed with the Lipoid PSP70-based cochleates, with a single oral dose of 7.5mg AmB/kg. Cochleates in both administration forms led to lower concentrations of Amphotericin B in the plasma than intravenous AmBisome®. However, more accumulation in the organs of interest (liver, spleen) was observed for both presentations of cochleates than for AmBisome® by the oral route. Therefore, cochleate formulations of AmB that could be produced at a cost accessible for developing countries show promise for the treatment of visceral leishmaniasis.

Ayaconin, a novel inhibitor of the plasma contact system from the sand fly Lutzomyia ayacuchensis, a vector of Andean-type cutaneous leishmaniasis.

Kawahori, S., Seki, C., Mizushima, D., Tabbabi, A., Yamamoto,

D., Kato, H.
08-07-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35817195

Transcriptome analysis of the salivary gland cDNA library from a phlebotomine sand fly, Lutzomyia ayacuchensis, identified a transcript coding for the PpSP15/SL1 family protein as the second most abundant salivary component. In the present study, a recombinant protein of the PpSP15/SL1 family protein, designated ayaconin, was expressed in Escherichia coli, and its biological activity was characterized. The recombinant ayaconin purified from the soluble fraction of E. coli lysate efficiently inhibited the intrinsic but not extrinsic blood coagulation pathway. When the target of ayaconin was evaluated using fluorescent substrates of coagulation factors, ayaconin inhibited factor XIIa (FXIIa) activity more efficiently in a dose-dependent manner, suggesting that FXII is the primary target of ayaconin. In addition, incubation of ayaconin with FXII prior to activation effectively inhibited FXIIa activity, whereas such inhibition was not observed when ayaconin was mixed after the production of FXIIa, indicating that ayaconin inhibits the activation process of FXII to produce FXIIa, but not the enzymatic activity of FXIIa. Moreover, ayaconin was shown to bind to FXII, suggesting that the binding of ayaconin to FXII is involved in the inhibitory mechanism against FXII activation. These results suggest that ayaconin plays an important role in the blood-sucking of Lu. ayacuchensis.

Miltefosine to Treat Childhood Cutaneous Leishmaniasis.

Barba, P., Morgado-Carrasco, D., Quera, A.
08-07-2022
Actas Dermosifiliogr
https://pubmed.ncbi.nlm.nih.gov/35817154

Serological and molecular detection of Leishmania species in dog peripheral blood from Bobo-Dioulasso city, a confirmation of canine leishmaniasis enzootic area for Burkina Faso.

Djibougou, A., Nikièma, A., Hien, A., Sangaré, I., Yameogo, B., Koala, L., Ouari, A., Diagbouga, S., Diabaté, A., Price, H., Fournet, F., Dabiré, R.
08-07-2022
Infect Genet Evol
https://pubmed.ncbi.nlm.nih.gov/35811035

Canine leishmaniasis is increasingly reported worldwide and represent a threat to both animal and human health. In a previous pilot study conducted in Bobo-Dioulasso, the second town of Burkina Faso, we reported five cases of canine leishmaniasis. With the perspective of a One Health action plan, and in the context of increasing urbanization, this study aimed to provide new information on Leishmania spp in dogs in this city. A cross-sectional survey was carried out from May to August 2018 in six districts of the city in order to record clinical and biological data from domestic dogs randomly selected per district. Blood samples were collected into EDTA tubes (4-5 mL), treated and stored at -20 °C until further analyses. The infection status of the dogs was performed by serological tests using plasma, and real time-PCR (RT-PCR) to detect Leishmania parasites using buffy coats. Nested PCR was used for typing the Leishmania species in dogs which were found to be RT-PCR positive. A total of 147 dogs were examined clinically and sampled for blood collection, including 53.7% females and 46.3% of males with a median age of 3 years. The seroincidence of Leishmania parasites within this dog population was 4.76% (95% CI:2.26-9.72). The incidence of Leishmania was 10.88% (95% CI: 6.73-17.11) by RT-PCR which was significantly more sensitive ($p = 0,047$) and a fair concordance was observed between both tests (Kappa = 0.39, $p < 0.001$). The characterization of Leishmania species revealed that L. major was circulating in this domestic dog population. Our results confirmed the persistence of zoonotic circulation of Leishmania parasites such as L. major currently in Bobo-Dioulasso city and highlight the need for targeted interventions in order to control transmission of leishmaniasis in this region.

Development and validation of a high-performance liquid chromatography tandem mass spectrometry method for the quantification of the antiparasitic and antifungal drug amphotericin B in human skin tissue.

Roseboom, I., Thijssen, B., Rosing, H., Alves, F., Sundar, S., Beijnen, J., Dorlo, T.
04-07-2022
J Chromatogr B Analyt Technol Biomed Life Sci
https://pubmed.ncbi.nlm.nih.gov/35810536

Amphotericin B is an antifungal and antiparasitic drug used in first-line treatment of the parasitic neglected tropical disease leishmaniasis. Liposomal amphotericin B is currently studied for the treatment of cutaneous and post-kala-azar dermal leishmaniasis, where the dermis of the skin is infected with Leishmania parasites. For the optimization of known treatment regimens, accurate target-site concentrations of the drug are required. To date, no assay was available to assess human skin concentrations of amphotericin B. We here present a bioanalytical assay for the quantification of amphotericin B in 4-mm human skin biopsies. Human skin biopsies were homogenized by overnight digestion using collagenase A and were processed afterwards by simple protein precipitation using methanol. Separation and detection were achieved using a Gemini C18 column with slightly acidic chromatographic conditions and a quadrupole - linear ion trap mass spectrometer, respectively. The method was validated in digestion solution over a range of 10-2,000 ng/mL using natamycin as internal standard, with a correlation coefficient (r^2) of at least 0.9974. The assay performance, accuracy and precision, were acceptable over the validated range, using international (EMA and FDA) acceptance criteria. In the skin tissue extracts, amphotericin B ion enhancement was observed, however, the internal standard (IS) corrected for this effect hence calibration

standards in digestion solvent could be used as a surrogate matrix for the quantification in skin tissue. Sample preparation recoveries were low (around 27%) because of degradation of amphotericin B during digestion and sample preparation processes, albeit highly reproducible, without compromising the accuracy and precision of the method. Using this assay, amphotericin B could be detected and quantified in skin biopsies originating from treated Indian post-kala-azar dermal leishmaniasis patients.

Treatment of Pediatric Cutaneous Leishmaniasis with Liposomal Amphotericin B.

Erat, T., An, I.
10-07-2022
Dermatol Ther
https://doi.org/10.1111/dth.15706

Background: The use of liposomal amphotericin B (L-AmB) in the treatment of cutaneous leishmaniasis (CL) is increasing. However, few data are available regarding the efficacy and safety of L-AmB in pediatric CL patients. Aims: Our aim in this study is to evaluate the efficacy and safety of L-AmB in pediatric CL patients. Methods: Pediatric patients admitted to a tertiary training and research hospital in a hyperendemic region for CL between January 2019 and May 2021 and receiving L-AmB therapy for CL were included in this retrospective study. L-AmB treatment was administered as 3 mg/kg for 5 consecutive days and on the 10th day, in a total of 6 doses (18 mg/kg total dose). Result: Fifty-two pediatric patients who received L-AmB therapy for CL were included in the study. In the follow-up 3 months after L-AmB treatment, 16 (31%) patients showed complete clinical recovery, while treatment failure was detected in 36 (69%) patients. Conclusion: In conclusion, considering the low treatment success rate in our study, we think that the L-AmB dose used in our study is not an appropriate treatment option for the treatment of pediatric CL patients. However, we think that prospective studies with a large number of patients treated with higher doses of L-AmB and in whom the causative agents of CL were determined are needed.

Biophysical and modeling-based approach for the identification of inhibitors against DOHH from Leishmania donovani.

Katiki, M., Sharma, M., Neetu, N., Rentala, M., Kumar, P.
09-07-2022
Brief Funct Genomics
https://pubmed.ncbi.nlm.nih.gov/35809341

The amino acid hypusine (Nε-4-amino-2-hydroxybutyl(lysine)) occurs only in isoforms of eukaryotic translation factor 5A (eIF5A) and has a role in initiating protein translation. Hypusinated eIF5A promotes translation and modulates mitochondrial function and oxygen consumption rates. The hypusination of eIF5A involves two enzymes, deoxyhypusine synthase and deoxyhypusine hydroxylase (DOHH). DOHH is the second enzyme that completes the synthesis of hypusine and the maturation of eIF5A. Our current study aims to identify inhibitors against DOHH from Leishmania donovani (LdDOHH), an intracellular protozoan parasite causing Leishmaniasis in humans. The LdDOHH protein was produced heterologously in Escherichia coli BL21(DE3) cells and characterized biochemically. The three-dimensional structure was predicted, and the compounds folic acid, scutellarin and homoarbutin were selected as top hits in virtual screening. These compounds were observed to bind in the active site of LdDOHH stabilizing the structure by making hydrogen bonds in the active site, as observed by the docking and molecular dynamics simulation studies. These results pave the path for further investigation of these molecules for their anti-leishmanial activities.

Global distribution of treatment resistance gene markers for leishmaniasis.

Revue de littérature

Salari, S., Bamorovat, M., Sharifi, I., Almani, P.
09-07-2022
J Clin Lab Anal
https://doi.org/10.1002/jcla.24599

Background: Pentavalent antimonials (Sb(V)) such as meglumine antimoniate (Glucantime®) and sodium stibogluconate (Pentostam®) are used as first-line treatments for leishmaniasis, either alone or in combination with second-line drugs such as amphotericin B (Amp B), miltefosine (MIL), methotrexate (MTX), or cryotherapy. Therapeutic aspects of these drugs are now challenged because of clinical resistance worldwide. Methods: We reviewedthe recent original studies were assessed by searching in electronic databases such as Scopus, Pubmed, Embase, and Web of Science. Results: Studies on molecular biomarkers involved in drug resistance are essential for monitoring the disease. We reviewed genes and mechanisms of resistance to leishmaniasis, and the geographical distribution of these biomarkers in each country has also been thoroughly investigated. Conclusion: Due to the emergence of resistant genes mainly in anthroponotic Leishmania species such as L. donovani and L. tropica, as the causative agents of ACL and AVL, respectively, selection of an appropriate treatment modality is essential. Physicians should be aware of the presence of such resistance for the selection of proper treatment modalities in endemic countries.

Biophysical and ultrasonographic changes of acute Old World cutaneous leishmaniasis skin lesions in comparison with uninvolved skin: A possible tool for non-invasive early detection and treatment outcome assessment.

Khatami, A., Yazdanparast, T., Ahmad Nasrollahi, S., Miramin Mohammadi, A., Yadangi, S., Khamesipour, A., Kassir, M., Firooz, A.
09-07-2022
Dermatol Ther
https://doi.org/10.1111/dth.15699

Background: Cutaneous leishmaniasis (CL) is a skin disease caused by intracellular protozoa, which is endemic in Iran. The goal of this study was to compare biophysical characteristics in CL lesions with uninvolved skin. **Methods:** Stratum corneum hydration, transepidermal water loss, surface friction, pH, sebum, melanin, erythema, temperature, elasticity parameters (R0, R2, and R5), thickness and echo-density of epidermis and dermis were measured on the active erythematous indurated part of a typical CL lesion in 20 patients, and compared with the same location on the other side of the body as control. Paired t- test was used for statistical analyses and a P<0.05 was considered significant. **Results:** Melanin content, R2 and echo-density of dermis were significantly lower, whereas transepidermal water loss, friction index, pH, erythema index, temperature and the thickness of dermis were significantly higher in CL lesions. There was no significant difference in stratum corneum hydration, sebum, R0, R5, thickness of epidermis and density of epidermis between CL and normal skin. **Conclusions:** CL lesions are characterized by certain changes in biophysical and ultrasonographic properties, which are mostly correlated with histological features. These changes are likely to be useful in the non-invasive early detection of CL and also as treatment outcome measures for clinical trials of new treatment modalities for CL in the future. This article is protected by copyright. All rights reserved.

Exploring the Immunotherapeutic Potential of Oleocanthal against Murine Cutaneous Leishmaniasis.

Karampetsou, K., Koutsoni, O., Badounas, F., Angelis, A., Gogou, G., Skaltsounis, L., Halabalaki, M., Dotsika, E.
08-07-2022
Planta Med
https://doi.org/10.1055/a-1843-9788

Leishmaniasis is a major tropical disease with increasing global incidence. Due to limited therapeutic options with severe drawbacks, the discovery of alternative treatments based on natural bioactive compounds is important. In our previous studies we have pointed out the antileishmanial activities of olive tree-derived molecules. In this study, we aimed to investigate the *in vitro* and *in vivo* antileishmanial as well as the *in vivo* immunomodulatory effects of oleocanthal, a molecule that has recently gained increasing scientific attention. Pure oleocanthal was isolated from extra virgin olive oil through extraction and chromatography techniques. The *in vitro* antileishmanial effects of oleocanthal were examined with a resazurin-based assay, while its *in vivo* efficacy was evaluated in *Leishmania major*-infected BALB/c mice by determining footpad induration, parasite load in popliteal lymph nodes, histopathological outcome, antibody production, cytokine profile of stimulated splenocytes and immune gene expression, at three weeks after the termination of treatment. Oleocanthal demonstrated *in vitro* antileishmanial effect against both *L. major* promastigotes and intracellular amastigotes. This effect was further documented *in vivo* as demonstrated by the suppressed footpad thickness, the decreased parasite load and the inflammatory cell influx at the infection site. Oleocanthal treatment led to the dominance of a Th1-type immunity linked with resistance against the disease. This study establishes strong scientific evidence for olive tree-derived natural products as possible antileishmanial agents and provides an adding value to the scientific research of oleocanthal.

Efficacy of intra-lesional injections of meglumine antimoniate once a week vs. twice a week in the treatment of cutaneous leishmaniasis caused by L. tropica in Iran: A randomized controlled clinical trial.

Javadi, A., Khamesipour, A., Ghoorchi, M., Bahrami, M., Khatami, A., Sharifi, I., Eskandari, S., Fekri, A., Aflatoonian, M., Firooz, A.
08-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010569

Treatment of Cutaneous leishmaniasis (CL) is based on using antimoniate derivatives; patients' compliance for systemic injections is low due to the pain and systemic complications. In this randomized open trial, the efficacy of intra-lesional (IL) injections of meglumine antimoniate (MA) once a week vs. twice a week in the treatment of Anthrpoponothic CL caused by L. tropica was studied. Eligible volunteer patients were selected according to inclusion/exclusion criteria. The included patients were randomly allocated to receive IL-MA injections once a week or twice a week. The primary outcome was set as complete healing of the lesion(s), and defined as complete re-epithelialization and absence of induration in the lesions. A total of 180 parasitologicaly proven CL patients caused by L. tropica were recruited, 90 patients were treated with weekly IL-MA and 90 patients received IL-MA twice a week. The complete cure was 87.9% vs. 89.2% in the group received weekly and twice a week IL-MA injections, respectively (P = 0.808). Patients' compliance was acceptable and side effects were limited to a few local allergic reactions to MA. Median time to healing was significantly shorter in patients who received IL-MA twice a week (median ± SE) 37±3.8, (CI: 29.6-44.4) days compared to whom received IL-MA once a week 60±2.3, (CI: 55.6-64.5) days (P< 0.001), however the number of injections was higher in group who received IL-MA twice a week (12 vs. 9 injections). In conclusion, the rate of cure in the group of CL patients with IL-MA twice a week was not significantly different from the group who received IL-MA once a week shorten, but the duration of healing was shorter in the group who received IL-MA twice a week while the group received more injections so is recommended to use IL-MA once a week due to the fact the compliance is acceptable with limited side effects. Clinical Trial Registration: IRCT20081130001475N13; https://en.irct.ir/.

Isolation, typing, and drug susceptibility of Leishmania (Leishmania) infantum isolates from dogs of the municipality of Embu das Artes, an endemic region for canine leishmaniasis in Brazil.

Ferreira, B., Martins, T., Coser, E., da L Oliveira, V., Yamashiro-Kanashiro, E., Rocha, M., Pinto, M., Cotrim, P., Coelho, A.
08-07-2022
Parasitol Res
https://doi.org/10.1007/s00436-022-07594-5

The parasitic protozoa Leishmania (Leishmania) infantum is the etiological agent of human visceral leishmaniasis and canine leishmaniasis in South America, where Brazil is the most affected country. This zoonotic disease is transmitted by the bite of an infected phlebotomine sand fly and dogs constitute the main domestic reservoir of the parasite. In this study, we screened 2348 dogs of the municipality of Embu das Artes, Brazil, for antibodies against the parasite. Prevalence for canine leishmaniasis seropositivity was 2.81%, as assessed using a Dual-Path Platform rapid test for canine leishmaniasis. Twenty-five seropositive dogs were euthanized for parasite isolation and 14 isolates were successful obtained. Nucleotide sequencing of the internal transcribed spacer confirmed the isolates to be L. (L.) infantum, and very low sequence variability was observed among them. The in vitro susceptibility to miltefosine and paromomycin was assessed and moderate variation in paromomycin susceptibility was found among the isolates in the promastigote and intracellular amastigote stages. On the other hand, in vitro susceptibility to miltefosine of these isolates was homogenous, particularly in the amastigote stage (EC_{50} values from 0.69 to 2.07 µM). In addition, the miltefosine sensitivity locus was deleted in all the isolates, which does not corroborate the hypothesis that the absence of this locus is correlated with a low in vitro susceptibility. Our findings confirm that the municipality of Embu das Artes is endemic for canine leishmaniasis and that isolates from this region are susceptible to paromomycin and miltefosine, indicating the potential of these drugs to be clinically evaluated in the treatment of human visceral leishmaniasis in Brazil.

Visceral Leishmaniasis: A Case Report of a Challenging Diagnosis After Orthotopic Liver Transplantation.

De Moraes Falcão, L., Ferraz, T., Brandão, R., Batista, A., Madeiro, V., Moura, F., Lyra, C.
04-07-2022
Transplant Proc
https://pubmed.ncbi.nlm.nih.gov/35798573

Leishmaniasis is a disease caused by a protozoan and transmitted by sandfly species in several emerging countries. Visceral leishmaniasis is a serious complication, especially in immunosuppressed patients, and is uncommon after liver transplantation. We report the case of a 48-year-old female patient who underwent liver transplantation owing to polycystic liver disease. Six months after the procedure, she was hospitalized with diarrhea, acute kidney failure, and leukopenia. She had been off steroids for 3 months and was taking mycophenolate and tacrolimus. She had already been treated for cytomegalovirus, which was negative on admission. During hospitalization, fever, splenomegaly, ascites, and pancytopenia appeared. Serology for Leishmania by indirect immunofluorescence was negative. Then, bone biopsy and molecular testing for Leishmania diagnosed it as visceral leishmaniasis. Amphotericin therapy was initiated with resolution of fever after 4 days of treatment and gradual recovery from pancytopenia. This case highlights the challenge of early diagnosis of visceral leishmaniasis in liver transplant recipients with diarrhea and leukopenia, which can be caused by immunosuppression or more prevalent viral diseases. Late onset of fever, splenomegaly, and a first negative serologic test also made early diagnosis difficult. The aim of the report is to emphasize the suspicion of visceral leishmaniasis in symptomatic patients from emerging countries and to question the benefit of including protozoan screening in liver transplant donors and recipients in endemic areas.

Evaluation of target-specific natural compounds for drug discovery against Leishmaniasis.

Revue de littérature

Gouri, V., Upreti, S., Samant, M.
05-07-2022
Parasitol Int
https://pubmed.ncbi.nlm.nih.gov/35798284

Leishmaniasis is a parasitic disease with no effective vaccine still now. Globally, it has affected millions of people, precisely in the undeveloped and developing countries. The control strategy for leishmaniasis depends only on chemotherapeutic methods that are associated with several side effects. Therefore, to overcome these negative impacts natural products are the best alternative for developing effective herbal-based drugs, which can act as one of the safest and effective alternative options to treat this particular disease. Leishmania, the causative agent of this disease possesses unique enzymes and metabolic pathways that are different from its mammalian host. Moreover, these unique enzymes, along with the signaling molecules and metabolic pathways that are crucial for its survival, serve as a suitable drug target for the evaluation of specific natural inhibitors to overcome leishmaniasis. Hence, in this review, we have discussed various specific targets of Leishmania, along with their natural inhibitors which can play a significant role in anti-leishmanial drug discovery.

Absolute configuration and antileishmanial activity of (-)-cyclocolorenone isolated from Duguetia lanceolata (Annonaceae).

Monteiro, J., Passero, L., Jesus, J., Laurenti, M., Lago, J., Soares, M., Batista, A., Batista, J., Sartorelli, P.
07-07-2022
Curr Top Med Chem
https://doi.org/10.2174/1568026622666220707095718

Background: The fractionation of the n-hexane phase of the EtOH extract from the leaves of Duguetia lanceolata (Annonaceae) led to the identification of the sesquiterpene (-)- cyclocolorenone. Objective: Chemical characterization,

including determination of the absolute stereochemistry, and in vitro evaluation of antileishmanial activity of the sesquiterpene (-)-cyclocolorenone, isolated from D. lanceolata were carried out. Methods: (-)-Cyclocolorenone was isolated from D. lanceolata leaves using different chromatographic steps and its structure was defined by analysis of NMR and ESI-HRMS data. Additionally, the absolute configuration of (-)-cyclocolorenone was ambiguously assigned by means of vibrational circular dichroism (VCD). Antileishmanial activity of (-)-cyclocolorenone was evaluated on promastigote and amastigote forms of Leishmania (Leishmania) amazonensis. The integrity of the cell membrane of L. (L.) amazonensis was analyzed using the SYTOX green probe. Results: (-)-(1R,6S,7R,10R)-Cyclocolorenone displayed activity against promastigotes and amastigotes forms of L. (L.) amazonensis with IC50 of 4.54 and 28.44 µM, respectively. Furthermore, this compound was non-toxic in J774 macrophage cells (CC50 > 458.71 µM) with a selectivity index > 100 (promastigotes) and > 32.2 (amastigotes). Additionally, (-)-cyclocolorenone was observed to target the parasite cell membrane. Conclusion: Obtained data suggested that (-)-cyclocolorenone, in which absolute configuration was determined, can be considered as a scaffold for the development of new drugs for the treatment of leishmaniasis.

The outcomes of polyparasitism in stray cats from Brazilian Midwest assessed by epidemiological, hematological and pathological data.

Silva, A., Andrade, G., Carvalho, J., Barreto, W., Santos, F., Sousa, K., André, M., Ferreira, L., Menezes, R., Herrera, H.
04-07-2022
Rev Bras Parasitol Vet
https://pubmed.ncbi.nlm.nih.gov/35792756

We evaluated the epidemiological, hematological, and pathological data of Leishmania spp., Toxoplasma gondii, Platynosomum illiciens, feline immunodeficiency virus (FIV), and feline leukemia virus (FeLV) infections and the coinfections in stray cats of an endemic area for leishmaniasis. The diagnosis was performed by serological tests and necropsy. We described gross lesions and histopathological findings. We used immunohistochemistry and chromogenic in situ hybridization for L. infantum detection. We found infection in 27 out of 50 sampled cats, among them, 14 presented coinfections. A strong correlation between splenomegaly and lymphadenomegaly with FeLV, and an association between hepatic lesions and cachexia with parasitism due to P. illiciens were observed. Moreover, we found a significant increase in the monocyte count in the FeLV-infected and a decrease in the red blood cell count in the FIV-infected animals. Amastigote forms of Leishmania spp. and tissue changes were detected in lymphoid organs of an animal coinfected with P. illiciens, T. gondii, and FIV. Polyparasitism recorded in stray cats of the Brazilian Midwest should be considered in effective control strategies for public health diseases. Moreover, stray cats of Campo Grande may be a source of infection of FIV, FeLV and P. illiciens for populations of domiciled cats.

In vivo transcriptional analysis of mice infected with Leishmania major unveils cellular heterogeneity and altered transcriptomic profiling at single-cell resolution.

Venugopal, G., Bird, J., Washam, C., Roys, H., Bowlin, A., Byrum, S., Weinkopff, T.
05-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010518

Leishmania parasites cause cutaneous leishmaniasis (CL), a disease characterized by disfiguring, ulcerative skin lesions. Both parasite and host gene expression following infection with various Leishmania species has been investigated in vitro, but global transcriptional analysis following L. major infection in vivo is lacking. Thus, we conducted a comprehensive transcriptomic profiling study combining bulk RNA sequencing (RNA-Seq) and single-cell RNA sequencing (scRNA-Seq) to identify global changes in gene expression in vivo following L. major infection. Bulk RNA-Seq analysis revealed that host immune response pathways like the antigen processing and presentation pathway were significantly enriched amongst differentially expressed genes (DEGs) upon infection, while ribosomal pathways were significantly downregulated in infected mice compared to naive controls. scRNA-Seq analyses revealed cellular heterogeneity including distinct resident and recruited cell types in the skin following murine L. major infection. Within the individual immune cell types, several DEGs indicative of many interferon induced GTPases and antigen presentation molecules were significantly enhanced in the infected ears including macrophages, resident macrophages, and inflammatory monocytes. Ingenuity Pathway Analysis of scRNA-Seq data indicated the antigen presentation pathway was increased with infection, while EIF2 signaling is the top downregulated pathway followed by eIF4/p70S6k and mTOR signaling in multiple cell types including macrophages, blood and lymphatic endothelial cells. Altogether, this transcriptomic profile highlights known recruitment of myeloid cells to lesions and recognizes a potential role for EIF2 signaling in murine L. major infection in vivo.

Benzylamines as highly potent inhibitors of the sterol biosynthesis pathway in Leishmania amazonensis leading to oxidative stress and ultrastructural alterations.

de Macedo-Silva, S., Visbal, G., Souza, G., Dos Santos, M., Cämmerer, S., de Souza, W., Rodrigues, J.
04-07-2022
Sci Rep
https://doi.org/10.1038/s41598-022-15449-3

Leishmaniasis is a neglected disease caused by protozoan parasites of the Leishmania genus. Benzylamines are a class of compounds selectively designed to inhibit the squalene synthase (SQS) that catalyzes the first committed reaction on the sterol biosynthesis pathway. Herein, we studied seven new benzylamines (SBC 37-43) against Leishmania

amazonensis. After the first screening of cell viability, two inhibitors (SBC 39 and SBC 40) were selected. Against intracellular amastigotes, SBC 39 and SBC 40 presented selectivity indexes of 117.7 and 180, respectively, indicating high selectivity. Analysis of the sterol composition revealed a depletion of endogenous 24-alkylated sterols such as episterol and 5-dehydroepisterol, with a concomitant accumulation of fecosterol, implying a disturbance in cellular lipid content. This result suggests a blockade of de novo sterol synthesis at the level of SQS and C-5 desaturase. Furthermore, physiological analysis and electron microscopy revealed three main alterations: (1) in the mitochondrion; (2) the presence of lipid bodies and autophagosomes; and (3) the appearance of projections in the plasma membrane. In conclusion, our results support the notion that benzylamines have a potent effect against Leishmania amazonensis and should be an exciting novel pharmaceutical lead for developing new chemotherapeutic alternatives to treat leishmaniasis.

Evaluation of the Prevalence of Malaria and Cutaneous Leishmaniasis in the Pre- and Post-Disaster Years in Iran.

Najjari, M., Rezaeian, S., Sheikhbardsiri, H., Afgar, A., Ebrahimipour, M.
04-07-2022
Prehosp Disaster Med
https://doi.org/10.1017/S1049023X22000942

Background/Objective: Natural disasters (NDs) are calamitous phenomena that can increase the risk of infections in disaster-affected regions. This study aimed to evaluate the frequency of malaria and cutaneous leishmaniasis (CL) before and after earthquakes, floods, and droughts during the past four decades in Iran. Methods: Malaria and CL data were obtained from the reports of the Ministry of Health and Medical Education in Iran for the years 1983 through 2017. The data of NDs were extracted from the Centre for Research on the Epidemiology of Disasters (CRED). Interrupted time series analysis with linear regression modeling was used to estimate time trends of mentioned diseases in pre- and post-disaster conditions. Results: For the periods preceding the disasters drought and flood, a decreasing time trend for malaria and CL was found over time. The time trend of malaria rate preceding the 1990 earthquake was stable, a downward trend was found after 1990 disaster until 1997 (β coefficient: -10.7; P = .001), and this declining trend was continued after 1997 disaster (β coefficient: -2.7; P = .001). The time trend of CL rate preceding the 1990 earthquake had a declining trend, an upward trend was found after 1990 earthquake until 1999 (β coefficient: +8.7; P = .293), and a slight upward trend had also appeared after 1999 earthquake (β coefficient: +0.75; P = .839). Conclusion: The results of the current study indicated the occurrence of earthquakes, floods, and droughts has no significant effect on the frequency of malaria and CL in Iran.

Essential Role of Enzymatic Activity in the Leishmanicidal Mechanism of the Eosinophil Cationic Protein (RNase 3).

Abengózar, M., Fernández-Reyes, M., Salazar, V., Torrent, M., de la Torre, B., Andreu, D., Boix, E., Rivas, L.
22-06-2022
ACS Infect Dis
https://doi.org/10.1021/acsinfecdis.1c00537

The recruitment of eosinophils into *Leishmania* lesions is frequently associated with a favorable evolution. A feasible effector for this process is eosinophil cationic protein (ECP, RNase 3), one of the main human eosinophil granule proteins, endowed with a broad spectrum of antimicrobial activity, including parasites. ECP was active on *Leishmania* promastigotes and axenic amastigotes (LC_{50}'s = 3 and 16 μM, respectively) but, in contrast to the irreversible membrane damage caused on bacteria and reproduced by its *N*-terminal peptides, it only induced a mild and transient plasma membrane destabilization on *Leishmania donovani* promastigotes. To assess the contribution of RNase activity to the overall leishmanicidal activity of ECP, parasites were challenged in parallel with a single-mutant version, ECP-H15A, devoid of RNase activity, that fully preserves the conformation and liposome permeabilization ability. ECP-H15A showed a similar uptake to ECP on promastigotes, but with higher LC_{50}'s (>25 μM) for both parasite stages. ECP-treated promastigotes showed a degraded RNA pattern, absent in ECP-H15A-treated samples. Moreover ECP, but not ECP-H15A, reduced more than 2-fold the parasite burden of infected macrophages. Altogether, our results suggest that ECP enters the *Leishmania* cytoplasm by an endocytic pathway, ultimately leading to RNA degradation as a key contribution to the leishmanicidal mechanism. Thus, ECP combines both membrane destabilization and enzymatic activities to effect parasite killing. Taken together, our data highlight the microbicidal versatility of ECP as an innate immunity component and support the development of cell-penetrating RNases as putative leishmanicidal agents.

Mucocutaneous Leishmaniasis due to Leishmania infantum Infection.

Linse, K., Bogdan, C., Haenssle, H., Toberer, F.
07-07-2022
Acta Derm Venereol
https://doi.org/10.2340/actadv.v102.2321

Exploration of 6-methyl-7-(Hetero)Aryl-7-Deazapurine ribonucleosides as antileishmanial agents.

Lin, C., Karalic, I., Matheeussen, A., Feijens, P., Hulpia, F., Maes, L., Caljon, G., Van Calenbergh, S.
25-04-2022
Eur J Med Chem
https://pubmed.ncbi.nlm.nih.gov/35533570

Leishmaniasis causes high mortality and morbidity in tropical

and subtropical regions of Africa, Asia, the Americas and southern Europe, and is characterized by diverse clinical manifestations. As a neglected tropical disease, limited resources are allocated for antileishmanial drug discovery. The Leishmania parasite is deficient in de novo purine synthesis, and therefore acquires purines from the host and processes these using a purine salvage pathway. By making use of purine transport systems and interfering with this salvage pathway, purine (nucleoside) analogues might exert a selective detrimental impact on its growth and survival. In vitro screening of an in-house purine nucleoside library and analogue synthesis afforded the 6-methyl-7-(2-pyridyl)-7-deazapurine ribonucleoside analogue 18 as a promising hit. Optimization of the 7-substituent afforded 31 and 32 which displayed potent activity against wild-type and resistant L. infantum, intracellular amastigote and extracellular promastigote forms, and favorable selectivity versus primary mouse macrophages (Mϕ) and MRC-5 cells. Encouraged by the favorable in vitro metabolic stability of 32, an in vivo study was performed using an early curative L. infantum hamster model. When orally administrated at 50 mg/kg once daily (s.i.d) for 10 days, 32 was devoid of side effects, however, it only poorly reduced amastigote burdens in the major target organs.

CYSTICERCOSE

Increased iron uptake in the bladder wall of racemose cysts of Taenia solium.

Orrego, M., Vasquez, C., Togneri, K., Laclette, J., Garcia, H., Nash, T., Cysticercosis Working Group in Peru
10-07-2022
Mol Biochem Parasitol
https://pubmed.ncbi.nlm.nih.gov/35830923

Racemose neurocysticercosis is an aggressive infection caused by the aberrant expansion and proliferation of the bladder wall of the Taenia solium cyst within the subarachnoid spaces of the human brain. The parasite develops and proliferates in a microenvironment with low concentrations of growth factors and micronutrients compared to serum. Iron is important for essential biological processes, but its requirement for racemose cyst viability and proliferation has not been studied. The presence of iron in the bladder wall of racemose and normal univesicular T. solium cysts was determined using Prussian blue staining. Iron deposits were readily detected in the bladder wall of racemose cysts but were not detectable in the bladder wall of univesicular cysts. Consistent with this finding, the genes for two iron-binding proteins (ferritin and melanotransferrin) and ribonucleotide reductase were markedly overexpressed in the racemose cyst compared to univesicular cysts. The presence of iron in the bladder wall of racemose cysts may be due to its increased metabolic rate due to proliferation.

DRACUNCULOSE

ECHINOCOCCOSE

The economic evaluation of Cystic echinococcosis control strategies focused on zoonotic hosts: A scoping review.

Widdicombe, J., Basáñez, M., Entezami, M., Jackson, D., Larrieu, E., Prada, J.
07-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010568

Background: Cystic echinococcosis (CE) is a zoonotic neglected tropical disease (zNTD) which imposes considerable financial burden to endemic countries. The 2021-2030 World Health Organization's roadmap on NTDs has proposed that intensified control be achieved in hyperendemic areas of 17 countries by 2030. Successful interventions for disease control, and the scale-up of programmes applying such interventions, rely on understanding the associated costs and relative return for investment. We conducted a scoping review of existing peer-reviewed literature on economic evaluations of CE control strategies focused on Echinococcus granulosus zoonotic hosts. Methodology/Principal findings: Database searches of Scopus, PubMed, Web of Science, CABI Direct and JSTOR were conducted and comprehensively reviewed in March 2022, using predefined search criteria with no date, field or language restrictions. A total of 100 papers were initially identified and assessed for eligibility against strict inclusion and exclusion criteria, following the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. Bibliography review of included manuscripts was used to identify additional literature. Full review of the final manuscript selection (n = 9) was performed and cost data for control interventions were extracted. Conclusions/Significance: There are very little published data pertaining to the cost and cost effectiveness of CE control interventions targeting its zoonotic hosts. Data given for costs are often incomplete, thus we were unable to perform an economic analysis and cost effectiveness study, highlighting a pressing need for this information. There is much scope for future work in this area. More detailed information and disaggregated costings need to be collected and made available. This would increase the accuracy of any cost-effective analyses to be performed and allow for a greater understanding of the opportunity cost of healthcare decisions and resource allocation by stakeholders and policy makers for effective and cost-effective CE control.

Prediction of benzimidazole therapy duration with PET/CT in inoperable patients with alveolar echinococcosis.

Husmann, L., Gruenig, H., Reiner, C., Deibel, A., Ledergerber, B., Liberini, V., Skawran, S., Muehlematter, U., Messerli, M., Hasse, B., Muellhaupt, B., Huellner, M.
06-07-2022
Sci Rep
https://doi.org/10.1038/s41598-022-15641-5

Alveolar echinococcosis is a rare parasitic disease, most frequently affecting the liver, as a slow-growing tumor-like lesion. If inoperable, long-term benzimidazole therapy is required, which is associated with high healthcare costs and occasionally with increased morbidity. The aim of our study was to determine the role ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in staging of patients with alveolar echinococcosis and to identify quantitative imaging parameters related to patient outcome and/or duration of benzimidazole therapy. In this single-center retrospective cohort study, 47 PET/CT performed for staging in patients with confirmed alveolar echinococcosis were analysed. In 43 patients (91%) benzimidazole therapy was initiated and was successfully stopped after a median of 870 days (766-2517) in 14/43 patients (33%). In inoperable patients, tests for trend of survivor functions displayed clear trends for longer benzimidazole therapy duration (p=0.05; n=25), and for longer time intervals to reach non-detectable serum concentration of Em-18 antibodies (p=0.01, n=15) across tertiles of SUVratio (maximum standardized uptake value in the echinococcus manifestation compared to normal liver tissue). Hence, in inoperable patients with alveolar echinococcosis, PET/CT performed for staging may predict the duration of benzimidazole therapy.

Hepatic Cysts: Reappraisal of the Classification, Terminology, Differential Diagnosis, and Clinicopathologic Characteristics in 258 Cases.

Armutlu, A., Quigley, B., Choi, H., Basturk, O., Akkas, G., Pehlivanoglu, B., Memis, B., Jang, K., Erkan, M., Erkan, B., Balci, S., Saka, B., Bagci, P., Farris, A., Kooby, D., Martin, D., Kalb, B., Maithel, S., Sarmiento, J., Reid, M., Adsay, N.
04-07-2022
Am J Surg Pathol
https://doi.org/10.1097/PAS.0000000000001930

The literature on liver cysts is highly conflicting, mostly owing to definitional variations. Two hundred and fifty-eight ≥1 cm cysts evaluated pathologically using updated criteria were classifiable as: I. Ductal plate malformation related (63%); that is, cystic bile duct hamartoma or not otherwise specified-type benign biliary cyst (35 with polycystic liver disease). These were female predominant (F/M=2.4), large (10 cm), often multifocal with degenerative/inflammatory changes and frequently misclassified as "hepatobiliary cystadenoma." II. Neoplastic (13%); 27 (10.5%) had ovarian-type stroma (OTS) and qualified as mucinous cystic neoplasm (MCN) per World Health Organization (WHO). These were female, solitary, mean age 52, mean size 11 cm, and 2 were associated with carcinoma (1 in situ and 1 microinvasive). There were 3 intraductal papillary neoplasms, 1 intraductal oncocytic papillary neoplasm, 1 cystic cholangiocarcinoma, and 2 cystic metastasis. III. Infectious/inflammatory (12%). These included 23 hydatid cysts (including 2 Echinococcus alveolaris both misdiagnosed preoperatively as cancer), nonspecific inflammatory cysts (abscesses, inflammatory cysts: 3.4%). IV. Congenital (7%). Mostly small (<3 cm); choledochal cyst (5%), foregut cyst (2%). V. Miscellaneous (4%). In conclusion, hepatic cysts occur predominantly in women (3/1), are mostly (90%) non-neoplastic, and seldom (<2%) malignant. Cystic bile duct hamartomas and their relative not otherwise specified-type benign biliary cysts are frequently multifocal and often misdiagnosed as "cystadenoma/carcinoma." Defined by OTS, MCNs (the true "hepatobiliary cystadenoma/carcinoma") are solitary, constitute only 10.5% of hepatic cysts, and have a significantly different profile than the impression in the literature in that essentially all are perimenopausal females, and rarely associated with carcinoma (7%). Since MCNs can only be diagnosed by demonstration of OTS through complete microscopic examination, it is advisable to avoid the term "cystadenoma/cystadenocarcinoma" solely based on radiologic examination, and the following simplified terminology would be preferable in preoperative evaluation to avoid conflicts with the final pathologic diagnosis: (1) noncomplex (favor benign), (2) complex (in 3 subsets, as favor benign, cannot rule out malignancy, or favor malignancy), (3) malignant features.

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

Differences in the secretory exosomes of Clonorchis sinensis adults at different incubation times.

Zhang, X., Duan, S., Li, X., Ding, J., Zuo, L., Sun, B., Zhang, X., Jiang, X., Gao, Y., Hu, X., Han, S.
09-07-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35820469

Exosomes are small vesicles of endocytic origin, which are released into the extracellular environment and mediate a variety of physiological and pathological conditions. Exosome-like vesicles (ELVs) have emerged recently as mediators in the parasite-parasite intercommunication and parasite-host interactions. Thus, increased knowledge of C. sinensis ELVs could provide insights into parasite-host interactions. In this experiment, ELVs was purified by ultracentrifugation from the culture medium of C. sinensis adults in vitro incubated for 24 h and 48 h, respectively. Transmission electron microscopy (TEM) and nanoparticle tracking analysis (NTA) confirmed that the purified vesicles which ranged from 30 to 150 nm in size were present in the culture medium. Small RNA high-

throughput sequencing analysis identified 51 miRNAs, including 37 known C. sinensis miRNAs, 3 novel C. sinensis miRNAs and 11 rat miRNAs. The sequencing data were validated by quantitative reverse transcription-polymerase chain reaction (RT-qPCR). The biological function of targets of known C. sinensis miRNAs were proved to associated with signal transduction, infectious diseases, and the immune system. Further, 15 miRNAs were classified as differentially expressed in the 24h-ELVs compared to the 48h-ELVs. We found that the numbers and expression levels of most miRNAs from 24h-ELVs were more and higer than 48h-ELVs'. Our work provides important data for understanding the molecular mechanisms underlying the pathogenesis of C. sinensis adults ELVs.

A machine learning approach using partitioning around medoids clustering and random forest classification to model groups of farms in regard to production parameters and bulk tank milk antibody status of two major internal parasites in dairy cows.

Oehm, A., Springer, A., Jordan, D., Strube, C., Knubben-Schweizer, G., Jensen, K., Zablotski, Y.
11-07-2022
PLoS One
https://doi.org/10.1371/journal.pone.0271413

Fasciola hepatica and Ostertagia ostertagi are internal parasites of cattle compromising physiology, productivity, and well-being. Parasites are complex in their effect on hosts, sometimes making it difficult to identify clear directions of associations between infection and production parameters. Therefore, unsupervised approaches not assuming a structure reduce the risk of introducing bias to the analysis. They may provide insights which cannot be obtained with conventional, supervised methodology. An unsupervised, exploratory cluster analysis approach using the k-mode algorithm and partitioning around medoids detected two distinct clusters in a cross-sectional data set of milk yield, milk fat content, milk protein content as well as F. hepatica or O. ostertagi bulk tank milk antibody status from 606 dairy farms in three structurally different dairying regions in Germany. Parasite-positive farms grouped together with their respective production parameters to form separate clusters. A random forests algorithm characterised clusters with regard to external variables. Across all study regions, co-infections with F. hepatica or O. ostertagi, respectively, farming type, and pasture access appeared to be the most important factors discriminating clusters (i.e. farms). Furthermore, farm level lameness prevalence, herd size, BCS, stage of lactation, and somatic cell count were relevant criteria distinguishing clusters. This study is among the first to apply a cluster analysis approach in this context and potentially the first to implement a k-medoids algorithm and partitioning around medoids in the veterinary field. The results demonstrated that biologically relevant patterns of parasite status and milk parameters exist between farms positive for F. hepatica or O. ostertagi, respectively, and negative farms. Moreover, the machine learning approach confirmed results of previous work and shed further light on the complex setting of associations a between parasitic diseases, milk yield and milk constituents, and management practices.

Fasciola spp. in Southeast Asia: a systematic review and meta-analysis protocol.

Hoang Quang, V., Levecke, B., Do Trung, D., Devleesschauwer, B., Lam, B., Polman, K., Callens, S., Dorny, P., Dermauw, V.
05-07-2022
Syst Rev
https://doi.org/10.1186/s13643-022-02013-3

Background: Fascioliasis is an emerging public health threat in a number of regions worldwide, including Southeast Asia. Up to now, a summary of current knowledge on the occurrence and the distribution in Southeast Asia is lacking. We therefore aim to gather recent information on the distribution and prevalence of and the associated risk factors for Fasciola spp. infections in humans, animals, and plant carriers in Southeast Asia. Methods: Bibliographic and gray literature databases as well as reference lists of important review articles will be searched for relevant records that are published between January 1, 2000, and the search date. The systematic review will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews. The primary outcomes will be both the prevalence of Fasciola spp. in the human and animal hosts, and on plant carriers in Southeast Asia, and the risk factors for occurrence of Fasciola spp. Secondary outcomes are the prevalence of Fasciola spp. in subpopulations (e.g., children and patients visiting clinics), the mapping of different diagnostic tests used, and the occurrence of the different Fasciola spp. in the study region. A descriptive statistical analysis will be conducted, and a meta-analysis will be run to estimate the prevalence of human and animal fascioliasis respectively, in Southeast Asia. Discussion: This systematic review will summarize the current knowledge on the epidemiology of Fasciola spp. infections in Southeast Asia. Systematic review registration: This systematic review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO), reference number: CRD42021261104 .

FILARIOSE LYMPHATIQUE

Historical overview and geographical distribution of neglected tropical diseases amenable to preventive chemotherapy in the Republic of the Congo: A systematic review.

Ngatse, J., Ndziessi, G., Missamou, F., Kinouani, R., Hemilembolo, M., Pion, S., Bork, K., Abena, A., Boussinesq, M., Chesnais, C.
11-07-2022

PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010560

Background: Neglected Tropical Diseases amenable to Preventive Chemotherapy (PC-NTDs) affect the poorest populations around the world, especially in Africa. Scientific information on the distribution and level of endemicity of these diseases in the Republic of the Congo (RoC) is scarce in the published literature. We sought to collect all available epidemiological data on PC-NTDs in the RoC to document the historical and current situation and identify challenges in reaching the elimination of NTDs. **Methods:** We searched Medline and Horizon databases for studies published until to July 4th, 2019, on onchocerciasis, lymphatic filariasis, soil-transmitted helminth infections, schistosomiasis, and trachoma in the RoC. Unpublished reports were also reviewed. We included all epidemiological studies containing community data and excluded case reports. Location, prevalence data, and dates of the studies were extracted. **Principal findings:** We identified 933 records, of which 56 met the inclusion criteria. The articles published before 1960 mainly concerned onchocerciasis and schistosomiasis. Despite a low number over the studied period, since 2005 there has been a steady increase in the number of publications. Most of the studies were cross-sectional and conducted in the general population. Trachoma is endemic in the Sangha and Likouala departments (prevalence of trachomatous inflammation-follicular > 5% in some villages), and further mapping is essential to properly assess the burden of this disease in the country. While the prevalence of soil-transmitted helminths is still high (over 20%) in a large part of Congo, cases of lymphatic filariasis (based on Wuchereria bancrofti antigenaemia and/or microfilaraemia) and onchocerciasis are becoming rare and very focused. To achieve the elimination of PC-NTDs, further intervention is required. **Conclusions:** Except for trachoma, whose epidemiological situation should be better evaluated, PC-NTDs are endemic in the RoC, and actions to control them have been taken by health authorities. To eliminate PC-NTDs, which are still present in some locations, new mapping surveys are needed, and increased investment in scientific research should be encouraged in the country.

Lymphatic filarial serum proteome profiling for identification and characterization of diagnostic biomarkers.

Kumar, V., Mishra, A., Yadav, A., Rathaur, S., Singh, A.
06-07-2022
PLoS One
https://doi.org/10.1371/journal.pone.0270635

Lymphatic Filariasis (LF) affects more than 863 million people in tropical and subtropical areas of the world, causing high morbidity and long illnesses leading to social exclusion and loss of wages. A combination of drugs Ivermectin, Diethylcarbamazine citrate and Albendazole is recommended by WHO to accelerate the Global Programme to Eliminate Lymphatic Filariasis (GPELF). To assess the outcome of GPELF, to re-evaluate and to formulate further strategies there is an imperative need for high quality diagnostic markers. This study was undertaken to identify Lymphatic Filarial biomarkers which can detect LF infections in asymptomatic cases and would also serve as indicators for differentiating among different clinical stages of the disease. A combination of Fourier-transform infrared spectroscopy (FT-IR), MMP zymography, SDS-PAGE, classical 2DE along with MALDI-TOF/MS was done to identify LF biomarkers from serum samples of different stages of LF patients. FT-IR spectroscopy coupled with univariate and multivariate analysis of LF serum samples, revealed significant differences in peak intensity at 3300, 2950, 1645, 1540 and 1448 cm-1 ($p<0.05$). The proteomics analysis results showed that various proteins were differentially expressed ($p<0.05$), including C-reactive protein, α-1-antitrypsin, heterogeneous nuclear ribonucleoprotein D like, apolipoproteins A-I and A-IV in different LF clinical stages. Functional pathway analysis suggested the involvement of differentially expressed proteins in vital physiological pathways like acute phase response, hemostasis, complement and coagulation cascades. Furthermore, the differentiation between different stages of LF cases and biomarkers identified in this study clearly demonstrates the potential of the human serum profiling approach for LF detection. To our knowledge, this is the first report of comparative human serum profiling in different categories of LF patients.

Semiannual Treatment of Albendazole Alone is Efficacious for Treatment of Lymphatic Filariasis: A Randomized Open-label Trial in Cote d'Ivoire.

Ouattara, A., Bjerum, C., Aboulaye, M., Kouadio, O., Marius, V., Andersen, B., Lew, D., Goss, C., Weil, G., Koudou, B., King, C.
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Clin Infect Dis
https://doi.org/10.1093/cid/ciab194

Background: Ivermectin (IVM) plus albendazole (ALB), or IA, is widely used in mass drug administration (MDA) programs that aim to eliminate lymphatic filariasis (LF) in Africa. However, IVM can cause severe adverse events in persons with heavy Loa loa infections that are common in Central Africa. ALB is safe in loiasis, but more information is needed on its efficacy for LF. This study compared the efficacy and safety of 3 years of semiannual treatment with ALB to annual IA in persons with bancroftian filariasis. **Methods:** Adults with Wuchereria bancrofti microfilaremia (Mf) were randomized to receive either 3 annual doses of IA (N = 52), 6 semiannual doses of ALB 400 mg (N = 45), or 6 semiannual doses of ALB 800 mg (N = 47). The primary outcome is amicrofilaremia at 36 months. **Results:** IA was more effective for completely clearing Mf than ALB 400mg or ALB 800mg (79%, 95% confidence interval [CI]: 67-91; vs 48%, 95% CI: 32-66 and 57%, 95% CI: 41-73, respectively). Mean percentage reductions in Mf counts at 36 months relative to baseline tended to be greater after IA (98%, 95% CI: 88-100) than after ALB 400 mg (88%, 95% CI: 78-98) and ALB 800 mg (89%, 95% CI: 79-99) (P = .07 and P = .06, respectively). Adult worm nest numbers (assessed by ultrasound) were reduced in all treatment groups. Treatments were well tolerated. **Conclusions:** Repeated semiannual

treatment with ALB is macrofilaricidal for W. bancrofti and leads to sustained reductions in Mf counts. This is a safe and effective regimen that could be used as MDA to eliminate LF in areas where ivermectin cannot be used. **Clinical Trials Registration:** NCT02974049.

MYCETOME

ONCHOCERCOSE

SCHISTOSOMIASE

Type 2 immunity: a two-edged sword in schistosomiasis immunopathology.

Revue de littérature

Abdel Aziz, N., Musaigwa, F., Mosala, P., Berkiks, I., Brombacher, F.
11-07-2022
Trends Immunol
https://pubmed.ncbi.nlm.nih.gov/35835714

Schistosomiasis is the second most debilitating neglected tropical disease globally after malaria, with no available therapy to control disease-driven immunopathology. Although schistosomiasis induces a markedly heterogenous immune response, type 2 immunity is the dominating immune response following oviposition. While type 2 immunity has a crucial role in granuloma formation and host survival during the acute stage of disease, its chronic activation can result in tissue scarring, fibrosis, and organ impairment. Here, we discuss recent advances in schistosomiasis, demonstrating how different immune and non-immune cells and signaling pathways are involved in the induction, maintenance, and regulation of type 2 immunity. A better understanding of these immune responses during schistosomiasis is essential to inform the potential development of candidate therapeutic strategies that fine-tune type 2 immunity to ideally modulate schistosomiasis immunopathology.

Schistosomiasis related circulating cell-free DNA: a useful biomarker in diagnostics.

Revue de littérature

Ullah, H., Arbab, S., Li, K., Khan, M., Qadeer, A., Muhammad, N.
11-07-2022
Mol Biochem Parasitol
https://pubmed.ncbi.nlm.nih.gov/35835258

Schistosoma is a genus of trematodes causing schistosomiasis, a major neglected tropical disease infecting more than 240 million people and with 700 million people at the risk of infection in the tropical and subtropical regions of the world, especially low-income countries. For the elimination of the disease, accurate diagnostic tools are needed. Besides allowing early treatment, early detection prevents environmental contamination and in turn ensures safe water sources in the endemic areas. Cell-free DNA (cfDNA) biomarker detection is a relatively new tool, used for the diagnosis of schistosomiasis in the early stages of infection from non-invasive clinical or experimental samples. cfDNA can be detected in Schistosoma infected host body fluids such as urine, serum, saliva and tissues, mainly in blood offering significant benefits for accurate diagnosis. In the current review, we described different characteristics of cfDNA, evidencing and supporting its potential uses in Schistosoma diagnosis and the improvement of treatment effectiveness.

Safety of Praziquantel and Albendazole Coadministration for the Control and Elimination of Schistosomiasis and Soil-Transmitted Helminths Among Children in Rwanda: An Active Surveillance Study.

Kabatende, J., Barry, A., Mugisha, M., Ntirenganya, L., Bergman, U., Bienvenu, E., Aklillu, E.
11-07-2022
Drug Saf
https://doi.org/10.1007/s40264-022-01201-3

Introduction: School-based preventive chemotherapy (Deworming) with praziquantel and albendazole to control and eliminate schistosomiasis and soil-transmitted helminths as public health problems is recommended by the World Health Organization (WHO). Safety monitoring during mass drug administration (MDA) is imperative but data from sub-Saharan Africa are scarce. **Objective:** The aim of this active safety surveillance study was to identify the incidence, type, severity, and risk factors for adverse events (AEs) following mass administration of praziquantel and albendazole. **Methods:** Overall, 8037 school children aged 5-15 years in Rwanda were enrolled. Baseline sociodemographic, medical history and any pre-existing clinical symptoms were recorded. Participants received a single dose of praziquantel and albendazole during MDA. AEs were actively monitored on days 1, 2, and 7 post MDA. **Results:** Overall, 3196 AEs were reported by 1658 children; 91.3%, 8.4%, and 0.3% of the AEs were mild, moderate, and severe, respectively, and most resolved within 3 days. Headache (21%), dizziness or fainting (15.2 %), nausea (12.8%) and stomach pain (12.2%) were the most common AEs. The overall cumulative incidence of experiencing at least one type of AE was 20.6% (95% confidence interval [CI] 19.7-21.5%), being significantly higher ($p < 0.001$) in children with pre-MDA clinical events (27.5%, 95% CI 25.4-29.6%) than those without (18.7%, 95% CI 17.7-19.7%). Females, older age, having pre-MDA events, types of food taken before MDA and taking two or more praziquantel tablets were significant predictors of AEs. **Conclusions:**

Praziquantel and albendazole MDA is safe and well-tolerated; however, one in five children experience transient mild to moderate, and in few cases severe, AEs. The incidence of AEs varies significantly between sex and age groups. Pharmacovigilance in the MDA program is recommended for timely detection and management of AEs.

Schistosoma mansoni infection decreases IL-33-mRNA expression and increases CXCL9 and CXCL10 production by peripheral blood cells.

do Nascimento, W., Nóbrega, C., Fernandes, E., Santos, P., Melo, F., Albuquerque, M., de Lorena, V., Costa, V., Barbosa, C., de Souza, V.
11-07-2022
Med Microbiol Immunol
https://doi.org/10.1007/s00430-022-00745-6

Schistosoma mansoni infections, particularly egg antigens, induce Th2-dominant granulomatous responses accompanied by remarkable immunoregulatory mechanisms that avoid intense fibrosis. Interleukin (IL)-33 is a cytokine that stimulates the early activation of Th2 responses, and its soluble ST2 receptor (sST2) avoids granulomatous response, as well as CXCL9 and CXCL10 chemokines that have antifibrotic activity. However, in schistosomiasis, these molecules have not been suitably studied. Therefore, this study aimed to measure IL-33 and sST2 RNA, cytokines, and chemokines in peripheral blood cultures from individuals living in schistosomiasis-endemic areas. Peripheral blood cells from individuals with S. mansoni (n=34) and non-infected individuals (n=31) were cultured under mitogen stimulation. Supernatant chemokines and cytokines were evaluated using a cytometric bead array, and IL-33 and sST2 mRNA expression was measured using qPCR. Infected individuals showed higher levels of CXCL8, CXCL9, CXCL10, IFN-γ, TNF-α, IL-6, IL-2, IL-4, and IL-10; there was a lower expression of IL-33 mRNA and similar expression of sST2mRNA in infected than non-infected individuals. In conclusion, for the first time, we demonstrated lower IL-33mRNA expression and high levels of the antifibrotic chemokines CXCL9 and CXCL10 in schistosomiasis mansoni, which could control exacerbations of the disease in individuals from endemic areas.

Historical overview and geographical distribution of neglected tropical diseases amenable to preventive chemotherapy in the Republic of the Congo: A systematic review.

Ngatse, J., Ndziessi, G., Missamou, F., Kinouani, R., Hemilembolo, M., Pion, S., Bork, K., Abena, A., Boussinesq, M., Chesnais, C.
11-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010560

Background: Neglected Tropical Diseases amenable to Preventive Chemotherapy (PC-NTDs) affect the poorest populations around the world, especially in Africa. Scientific information on the distribution and level of endemicity of these diseases in the Republic of the Congo (RoC) is scarce in the published literature. We sought to collect all available epidemiological data on PC-NTDs in the RoC to document the historical and current situation and identify challenges in reaching the elimination of NTDs. **Methods:** We searched Medline and Horizon databases for studies published until to July 4th, 2019, on onchocerciasis, lymphatic filariasis, soil-transmitted helminth infections, schistosomiasis, and trachoma in the RoC. Unpublished reports were also reviewed. We included all epidemiological studies containing community data and excluded case reports. Location, prevalence data, and dates of the studies were extracted. **Principal findings:** We identified 933 records, of which 56 met the inclusion criteria. The articles published before 1960 mainly concerned onchocerciasis and schistosomiasis. Despite a low number over the studied period, since 2005 there has been a steady increase in the number of publications. Most of the studies were cross-sectional and conducted in the general population. Trachoma is endemic in the Sangha and Likouala departments (prevalence of trachomatous inflammation-follicular > 5% in some villages), and further mapping is essential to properly assess the burden of this disease in the country. While the prevalence of soil-transmitted helminths is still high (over 20%) in a large part of Congo, cases of lymphatic filariasis (based on Wuchereria bancrofti antigenaemia and/or microfilaraemia) and onchocerciasis are becoming rare and very focused. To achieve the elimination of PC-NTDs, further intervention is required. **Conclusions:** Except for trachoma, whose epidemiological situation should be better evaluated, PC-NTDs are endemic in the RoC, and actions to control them have been taken by health authorities. To eliminate PC-NTDs, which are still present in some locations, new mapping surveys are needed, and increased investment in scientific research should be encouraged in the country.

Identification of a linear B-cell epitope on the Schistosoma japonicum saposin protein, SjSAP4: Potential as a component of a multi-epitope diagnostic assay.

Mu, Y., Gordon, C., Olveda, R., Ross, A., Olveda, D., Marsh, J., McManus, D., Cai, P.
11-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010619

Background: Schistosoma japonicum is one of three major species of blood flukes causing schistosomiasis, a disease, which continues to be a major public health issue in the Philippines. SjSAP4, a member of a multigene family of saposin-like proteins, is a recognized immunodiagnostic biomarker for schistosomiasis japonica. This study aimed to identify linear B-cell epitopes on SjSAP4 and to validate their potential as components of a multi-epitope assay for the serological diagnosis of schistosomiasis japonica. **Methodology:** SjSAP4-dereived peptides were expressed as GST-peptide-fused proteins and these were Western blot probed with human serum samples from S. japonicum Kato-

Katz (KK)-positive individuals and uninfected controls. A core epitope was further identified by Western blotting through probing a series of truncated peptides with the schistosomiasis patient sera. The diagnostic performance of the core epitope-containing peptides and the full-length SjSAP4 was evaluated by enzyme-linked immunosorbent assay (ELISA) using a panel of sera collected from subjects resident in a schistosomiasis-endemic area of the Philippines. **Main findings:** As a result of the peptide mapping, one peptide (P15) was found to be highly immunogenic in the KK-positive individuals. We subsequently showed that -S163QCSLVGDIFVDKYLD178- is a core B-cell epitope of P15. Subsequent ELISAs incorporating rSjSAP4, SjSAP4-Peptide and SjSP-13V2-Peptide showed a sensitivity of 94.0%, 46.0% and 74.0%, respectively, and a specificity of 97.1%, 100% and 100%, respectively. Notably, complementary recognition of the B-cell epitopes (SjSAP4-Peptide and SjSP-13V2-Peptide) was observed in a subset of the KK-positive individuals. A dual epitope-ELISA (SjSAP4-Peptide + SjSP-13V2-Peptide-ELISA) showed a diagnostic sensitivity of 84.0% and a specificity of 100%. **Conclusions/Significance:** In this study, -S163QCSLVGDIFVDKYLD178- was identified as a dominant linear B-cell epitope on SjSAP4. This peptide and the complementary recognition of other B-cell epitopes using sera from different KK-positive individuals can provide the basis of developing a multi-epitope assay for the serological diagnosis of schistosomiasis.

Ethical and practical considerations arising from community consultation on implementing controlled human infection studies using *Schistosoma mansoni* in Uganda.

Egesa, M., Ssali, A., Tumwesige, E., Kizza, M., Driciru, E., Luboga, F., Roestenberg, M., Seeley, J., Elliott, A.
04-07-2022
Glob Bioeth
https://doi.org/10.1080/11287462.2022.2091503

Issues related to controlled human infection studies using *Schistosoma mansoni* (CHI-S) were explored to ensure the ethical and voluntary participation of potential CHI-S volunteers in an endemic setting in Uganda. We invited volunteers from a fishing community and a tertiary education community to guide the development of informed consent procedures. Consultative group discussions were held to modify educational materials on schistosomiasis, vaccines and the CHI-S model and similar discussions were held with a test group. With both groups, a mock consent process was conducted. Fourteen in-depth key informant interviews and three group discussions were held to explore perceptions towards participating in a CHI-S. Most of the participants had not heard of the CHI-S. Willingness to take part depended on understanding the study procedures and the consenting process. Close social networks were key in deciding to take part. The worry of adverse effects was cited as a possible hindrance to taking part. Volunteer time compensation was unclear for a CHI-S. Potential volunteers in these communities are willing to take part in a CHI-S. Community engagement is needed to build trust and time must be taken to share study procedures and ensure understanding of key messages.

Genome-wide identification of circular RNAs in adult Schistosoma japonicum.

Giri, B., Fang, C., Cheng, G.
07-07-2022
Int J Parasitol
https://pubmed.ncbi.nlm.nih.gov/35810786

Circular RNAs (circRNAs) are a class of novel, widespread, covalently closed RNAs that have played an essential role in animal gene regulation. To systematically explore circRNAs in the blood fluke Schistosoma japonicum, we performed RNA sequencing and bioinformatics analysis, and found that hundreds of circRNAs showed gender-associated expression. Among these identified circRNAs, more than 77.54% and 74.73% were putatively derived from the exon region of the genome and some circRNAs showed gender-associated expressions. The functional prediction of circRNAs (circ_003826 and circ_004690) showed potential binding sites and possibly acted as the sponge to regulate microRNAs (miRNAs) sja-miR-1, sja-miR-133 and sja-miR-3504. Altogether, these findings demonstrated that S. japonicum also contains circRNAs, which may have potential regulatory roles during schistosome development.

Absence of lower genital tract lesions among women of reproductive age infected with Schistosoma mansoni: A cross-sectional study using a colposcope in Western Kenya.

Sang, H., Mwinzi, P., Odiere, M., Onkanga, I., Rawago, F., Pillay, P., Kjetland, E.
08-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010473

Background: Female genital schistosomiasis (FGS) constitutes four different lesions known to be caused by Schistosoma haematobium ova deposited in the genital tract. Schistosoma mansoni ova may also be found in the genital tract. However, it is not known if S. mansoni causes lower genital tract lesions characteristic of FGS. **Methodology:** This study was conducted in 8 villages along the shores of Lake Victoria, western Kenya. Stool and urine samples collected from women of reproductive age on three consecutive days were analysed for S. mansoni and S. haematobium infection. S. mansoni positive and S. haematobium negative willing participants, aged 18-50 years were invited to answer a questionnaire (demographics, symptoms), undergo a gynaecological examination and cytology specimen collection by an FGS expert. **Principal findings:** Gynaecologic investigations were conducted in 147 S. mansoni-positive women who had a mean infection intensity of 253.3 epg (95% CI: 194.8-311.9 epg). Nearly 90% of them used Lake Victoria as their main water source. None were found to have cervicovaginal grainy sandy patches or rubbery papules. Homogenous yellow patches were found in 12/147

(8.2%) women. Women with homogenous yellow patches were significantly older (47 years) than the rest (34 years, p = 0.001). No association was found between intensity of S. mansoni infection and homogenous yellow patches (p = 0.70) or abnormal blood vessels (p = 0.14). S. mansoni infection intensity was not associated with genital itch, bloody or malodorous vaginal discharge. **Conclusion:** S. mansoni infection was neither associated with lower genital tract lesions nor symptoms typically found in women with FGS.

Reduction in DALYs lost due to soil-transmitted helminthiases and schistosomiasis from 2000 to 2019 is parallel to the increase in coverage of the global control programmes.

Montresor, A., Mwinzi, P., Mupfasoni, D., Garba, A.
07-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010575

Preventive chemotherapy interventions for the control of soil-transmitted helminthiases (STH) and schistosomiasis scaled up from a global coverage level of around 5% in the year 2000 to a coverage that surpassed 60% in the year 2019. The present paper analyses the concomitant reduction in the number of disability-adjusted life years (DALYs) lost due to STH and schistosomiasis during the same period, from 6.3 to 3.5 million DALYs. The cumulative gain during the 19-year period was estimated at over 26 million DALYs. Given the low cost of the intervention, our study suggests that deworming for STH and schistosomiasis is one of the most cost-effective public health interventions.

Tropical Parasitic Itch in Returned Travelers and Immigrants from Endemic Areas.

Revue de littérature

Ju, T., Vander Does, A., Ingrasci, G., Norton, S., Yosipovitch, G.
06-07-2022
J Eur Acad Dermatol Venereol
https://doi.org/10.1111/jdv.18408

Itch is the most common skin symptom among tropical parasitic diseases (TPD) but there are limited data about its characteristics in these conditions. In dermatology practices and travelers' health clinics in the developed world, itch is a common complaint among travelers returning from endemic areas, as well among migrants arriving from endemic areas, where they may have been exposed to TPD. Studying aspects of pruritus among TPD may lead to improvements in prompt, accurate diagnosis and management of these conditions. This review examines the major itch-inducing TPDs, including schistosomiasis, echinococcosis, onchocerciasis, scabies, cutaneous larva migrans, larva currens, African trypanosomiasis, dracunculiasis, and other causes of travel associated pruritus. We focus on the link between pruritus and other symptoms, etiology, clinical staging, and therapy options for these parasitic illnesses. Because some tropical parasitic diseases can present with significant pruritus, we attempt to identify aspects of the pruritus that are characteristic of-or unique to-specific conditions. These diagnostic insights may help clinicians create a rational and focused differential diagnosis and help determine optimal disease management pathways. In this sense, management involves treating the individual, seeking epidemiologically linked cases, preventing recurrences or relapses, and reducing spread of the disease.

Prevalence of malaria and helminth infections in rural communities in northern Sierra Leone, a baseline study to inform Ebola vaccine study protocols.

Baiden, F., Fleck, S., Leigh, B., Ayieko, P., Tindanbil, D., Otieno, T., Lawal, B., Tehtor, M., Rogers, M., Odeny, L., Hodges, M., Sonnie, M., Samai, M., Ishola, D., Lowe, B., Watson-Jones, D., Greenwood, B.
06-07-2022
PLoS One
https://doi.org/10.1371/journal.pone.0270968

Introduction: Recurrent parasitic infections may influence the immune response to vaccines. In the Partnership for Research on Ebola VACcinations extended follow-UP and clinical research capacity build-UP (PREVAC-UP) study being undertaken in Mambolo, northern Sierra Leone, participants are being followed up to assess the potential impact of exposure to malaria and/or helminth infections on long-term immune response to two Ebola vaccines. To support the development of the assays that will be used in this evaluation, a parasitological survey was conducted in Mambolo between November 2019 and February 2020. **Methods:** Healthy individuals aged ≥1 year who were resident in Mambolo Chiefdom were selected using a stratified sampling approach and questionnaires were administered to explore their sociodemographic characteristics. Microscopy was used to detect malaria parasites, intestinal helminths and urinary schistosome infections. Rapid blood tests were used to detect infections with Onchocerca volvulus and Wuchereria bancrofti. We estimated the overall prevalence of these infections and used adjusted logistic regression models to explore risk factors for malaria and hookworm infection. **Results:** Eight hundred and fifteen (815) residents, 50.9% of whom were female were surveyed. Overall, 309 (39.1%) of 791 persons tested for malaria had a positive blood slide; Plasmodium falciparum was the dominant species. Helminth infection was detected in 122 (15.0%) of 815 stool samples including three mixed infections. The helminth infections comprised 102 (12.5%) cases of hookworm, 11 (1.3%) cases of Trichuris trichiura, 10 (1.2%) cases of Schistosoma mansoni and two (0.2%) cases of Ascaris lumbricoides. Being male (OR = 2.01, 95% CI 1.15-3.50) and residing in a non-riverine community (OR = 4.02, 95%CI 2.32-6.98) were the factors associated with hookworm infection. Onchocerca volvulus and Wuchereria bancrofti infections were found in 3.3% and 0.4% of participants respectively. **Conclusion:** Malaria and hookworm are the most prevalent parasite infections and those most likely to influence long-term immune response to Ebola vaccines among the trial participants.

Biochemical characterization and peptide mass fingerprinting of two glutathione transferases from Biomphalaria alexandrina snails (Gastropoda: Planorbidae).

Abdalla, A., Abdel Karim, G.
06-07-2022
J Genet Eng Biotechnol
https://doi.org/10.1186/s43141-022-00372-x

Background: The freshwater snails Biomphalaria alexandrina (Gastropoda: Planorbidae) has public health importance of being an intermediate host of Schistosoma mansoni, the parasite species that causes intestinal schistosomiasis in humans. Glutathione transferases (GSTs) play an important role in detoxification of a broad range of compounds including secondary metabolites and exogenous compounds. Studying GSTs in snails may clarify their role in detoxification of molluscicides. **Results:** Two glutathione transferases (BaGST2 and BaGST3) were purified and characterized from B. alexandrina snails. BaGST2 and BaGST3 were electrophoretically homogeneous preparations with subunit molecular weight of 23.6 kDa and molecular weight of 45 kDa. Isoelectric focusing of BaGST2 revealed the presence of two components at pI 4.47 and 4.67, while BaGST3 showed one band at pI 4.17. The specific activity of BaGST2 and BaGST3 toward 1-chloro-2,4-dinitrobenzene (CDNB) was 19.0 and 45.2 µmol/min/mg protein following 146- and 346-fold purification, respectively. The catalytic pH optima, km values, and the activation energies for BaGST2 and BaGST3 were determined. BaGST2 and BaGST3 were significantly inhibited by hematin and Cibacron Blue and to a less extent by bromosulfophthalein, S-butyl-GSH, S-hexyl-GSH, and S-P-bromobenzyl-GSH. BaGST2 and BaGST3 showed high activity against ethacrynic acid as substrate, and they also exhibited peroxidase activity on cumene hydroperoxide. The two enzymes showed identical patterns of lysine-C digestion after high-performance liquid chromatography. The amino acid sequences of three peptide fragments and peptide mass fingerprinting of fourteen peptides were used to predict the primary structure of BaGST2. A polypeptide of 206 amino acids (with 7 gaps, 3 of which could not identified) was predicted for BaGST2. The theoretical subunit molecular weight of BaGST2 is 22.6 kDa, with pI of 8.58. BaGST2 has 65% sequence identity and 78% positive with Biomphalaria glabrata GST7. The overall structure of BaGST2 at the N-terminal domain is identical to the canonical GST N-terminal domain, having the typical thioredoxin-like fold with a βαβ-α-ββα motif, whereas the C-terminal domain is made from 6 α-helices. A conservative GST-N-domain includes glutathione binding sites Y11, L17, Q53, M54, Q65, and S66, while a variable GST-C domain contains electrophilic substrate binding site H99, R102, A103, F106, K107, L161, and Y167. Phylogenetic tree showed that BaGST2 was clustered in the sigma group with GSTs sigma class from invertebrates and vertebrates. **Conclusions:** We have purified and characterized two GSTs from B. alexandrina snails. Our study broadens the biochemical information on freshwater snail GSTs by demonstrating the role of BaGSTs in defense mechanisms against structurally different electrophilic compounds. BaGST2 and BaGST3 have Se-independent peroxidase activity, which indicates their role in cellular antioxidant defense by reducing organic hydroperoxides in B. alexandrina. A polypeptide chain of 206 amino acids was predicted. The primary structure of BaGST2 showed 65% sequence identity with Biomphalaria glabrata GST7. Sequence analysis indicates that BaGST2 is a GST-N-sigma-like with a thioredoxin-like superfamily. Phylogenetic tree confirms that BaGST2 belongs to the sigma class of GSTs superfamily.

Cervical lesion proportion measure using a digital gridded imaging technique to assess cervical pathology in women with genital schistosomiasis.

Arenholt, L., Aaroe, K., Norderud, K., Lumholdt, M., Randrianasolo, B., Ramarokoto, C., Rabozakandraina, O., Broennum, D., Feldmeier, H., Leutscher, P.
05-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0009995

Female genital schistosomiasis (FGS) is characterized by a pattern of lesions which manifest at the cervix and the vagina, such as homogeneous and grainy sandy patches, rubbery papules in addition to neovascularization. A tool for quantification of the lesions is needed to improve FGS research and control programs. Hitherto, no tools are available to quantify clinical pathology at the cervix in a standardized and reproducible manner. This study aimed to develop and validate a cervical lesion proportion (CLP) measure for quantification of cervical pathology in FGS. A digital imaging technique was applied in which a grid containing 424 identical squares was positioned on high resolution digital images from the cervix of 70 women with FGS. CLP was measured for each image by observers counting the total number of squares containing at least one type of FGS associated lesion. For assessment of inter- and intra-observer reliability, three different observers measured CLP independently. In addition, a rubbery papule count (RPC) was determined in a similar manner. The intraclass correlation coefficient was 0.94 (excellent) for the CLP inter-rater reliability and 0.90 (good) for intra-rater reliability and the coefficients for the RPC were 0.88 and 0.80 (good), respectively. The CLP facilitated a reliable and reproducible quantification of FGS associated lesions of the cervix. In the future, grading of cervical pathology by CLP may provide insight into the natural course of schistosome egg-induced pathology of the cervix and may have a role in assessing praziquantel treatment efficacy against FGS. Trial Registration: ClinicalTrials.gov, trial number NCT04115072; trial URL https://clinicaltrials.gov/ct2/show/NCT04115072?term=Female+genital+schistosomiasis+AND+Madagascar&draw=2&rank=1.

Transmission and diversity of Schistosoma haematobium and S. bovis and their freshwater intermediate snail hosts Bulinus globosus and B. nasutus in the Zanzibar Archipelago, United Republic of Tanzania.

Pennance, T., Ame, S., Amour, A., Suleiman, K., Muhsin, M., Kabole, F., Ali, S., Archer, J., Allan, F., Emery, A., Rabone, M., Knopp, S., Rollinson, D., Cable, J., Webster, B.
05-07-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010585

Background: The Zanzibar Archipelago (Pemba and Unguja islands) is targeted for the elimination of human urogenital schistosomiasis caused by infection with Schistosoma haematobium where the intermediate snail host is Bulinus globosus. Following multiple studies, it has remained unclear if B. nasutus (a snail species that occupies geographically distinct regions on the Archipelago) is involved in S. haematobium transmission on Zanzibar. Additionally, S. haematobium was thought to be the only Schistosoma species present on the Zanzibar Archipelago until the sympatric transmission of S. bovis, a parasite of ruminants, was recently identified. Here we re-assess the epidemiology of schistosomiasis on Pemba and Unguja together with the role and genetic diversity of the Bulinus spp. involved in transmission. Methodology/Principal findings: Malacological and parasitological surveys were conducted between 2016 and 2019. In total, 11,116 Bulinus spp. snails were collected from 65 of 112 freshwater bodies surveyed. Bulinus species identification were determined using mitochondrial cox1 sequences for a representative subset of collected Bulinus (n = 504) and together with archived museum specimens (n = 6), 433 B. globosus and 77 B. nasutus were identified. Phylogenetic analysis of cox1 haplotypes revealed three distinct populations of B. globosus, two with an overlapping distribution on Pemba and one on Unguja. For B. nasutus, only a single clade with matching haplotypes was observed across the islands and included reference sequences from Kenya. Schistosoma haematobium cercariae (n = 158) were identified from 12 infected B. globosus and one B. nasutus collected between 2016 and 2019 in Pemba, and cercariae originating from 69 Bulinus spp. archived in museum collections. Schistosoma bovis cercariae (n = 21) were identified from seven additional B. globosus collected between 2016 and 2019 in Pemba. By analysing a partial mitochondrial cox1 region and the nuclear ITS (1-5.8S-2) rDNA region of Schistosoma cercariae, we identified 18 S. haematobium and three S. bovis haplotypes representing populations associated with mainland Africa and the Indian Ocean Islands (Zanzibar, Madagascar, Mauritius and Mafia). Conclusions/Significance: The individual B. nasutus on Pemba infected with S. haematobium demonstrates that B. nasutus could also play a role in the local transmission of S. haematobium. We provide preliminary evidence that intraspecific variability of S. haematobium on Pemba may increase the transmission potential of S. haematobium locally due to the expanded intermediate host range, and that the presence of S. bovis complicates the environmental surveillance of schistosome infections.

Carvedilol as secondary prophylaxis for variceal bleeding in hepatosplenic schistosomiasis.

de Abreu, E., Nardelli, M., Lima, A., Cardoso, J., Osório, F., Ferrari, T., Faria, L., Couto, C., Cançado, G.
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Trans R Soc Trop Med Hyg
https://doi.org/10.1093/trstmh/trab190

Background: Upper variceal bleeding (UVB) is a possible complication of portal hypertension secondary to hepatosplenic schistosomiasis (HSS). Propranolol is a non-selective beta-blocker used as secondary prophylaxis for UVB, but no previous studies have addressed carvedilol effects in rebleeding prevention. Methods: A retrospective exploratory study of 57 patients with chronic HSS and index UVB treated with endoscopic variceal ligation and propranolol or carvedilol was conducted. The primary outcome was UVB-free time in the first 12 mo after the initial bleeding episode. Results: Propranolol was used for secondary UVB prophylaxis in 43 (75.4%) participants (median dose 80 [interquartile range - IQR 60-80] mg/d) and carvedilol in 14 (24.6%) participants (median dose 12.5 [IQR 7.9-25.0] mg/d). During a 12-mo follow-up, rebleeding was observed in 13 (22.8%) patients, 9 (20.9%) of those treated with propranolol and 4 (28.6%) treated with carvedilol (p=0.715). Mean time from the beginning of drug prophylaxis to rebleeding was 6±3 mo and there was no difference between that for propranolol vs carvedilol subgroups. Portal vein thrombosis did not influence the bleeding recurrence in either subgroup. Conclusion: Carvedilol may be equally effective as propranolol in preventing secondary UVB in HSS at 12-mo follow-up.

Effectiveness of Four Different Interventions Against Schistosoma haematobium in a Seasonal Transmission Setting of Côte d'Ivoire: A Cluster Randomized Trial.

Ouattara, M., Bassa, F., Diakité, N., Hattendorf, J., Coulibaly, J., Yao, P., Tian-Bi, Y., Konan, C., Assaré, R., Koné, N., Guindo-Coulibaly, N., Utzinger, J., N'Goran, E.
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Clin Infect Dis
https://doi.org/10.1093/cid/ciab787

Background: Annual mass drug administration (MDA) using praziquantel is the cornerstone of schistosomiasis morbidity control but is not sufficient to interrupt transmission. We implemented a cluster-randomized trial to compare the effectiveness of 4 different intervention packages to interrupt transmission of Schistosoma haematobium in a seasonal transmission setting of Côte d'Ivoire. Methods: Sixty-four localities with a S. haematobium prevalence in school children aged 13-14 years above 4% were randomly assigned to 1 of 4 intervention arms over a 3-year period: (1) the current standard strategy consisting of annual MDA before peak of transmission, (2) annual MDA after peak of transmission, (3) biannual MDA, and (4) standard MDA combined with snail control. The primary outcome was prevalence and intensity of S. haematobium infection in children aged 9-12 years 1 year after the final intervention, using urine filtration performed by experienced microscopists. Results: By study end, we observed the lowest S. haematobium prevalence in the biannual MDA,

compared to the standard treatment arm (0.6% vs 7.5%; odds ratio [OR] = 0.07, 95% confidence interval [CI] = .02 to .24). The prevalence in arms 2 and 4 was about 3.5%, which was not statistically significantly different from the standard strategy (both ORs 0.4, 95% CI = .1 to ~1.8). New cases of infection were still observed in all arms at study end. **Conclusions:** Biannual MDA was the only regimen that outperformed the standard treatment. All strategies resulted in decreased prevalence of infection; however, none of them was able to interrupt transmission of S. haematobium within a 3-year period. **Clinical Trials Registration:** ISRCTN10926858.

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

Epidemiology of soil-transmitted helminthiasis and associated malnutrition among under-fives in conflict affected areas in southern Ethiopia.

Geleto, G., Kassa, T., Erko, B.
11-07-2022
Trop Med Health
https://doi.org/10.1186/s41182-022-00436-1

Background: Globally, there were about 50.8 million internally displaced people in 2020, of whom 42% were in sub-Saharan Africa. In areas where there are conflicts, the humanitarian emergency makes infectious disease management extremely complex. Soil-transmitted helminths (STHs) are among the most common infections globally including in Ethiopia that thrives during complex emergencies. However, with regards to STHs, studies in the context of conflict areas have not been documented in Ethiopia. **Methods:** In southern Ethiopia, a community-based cross-sectional study design was employed. Simple random sampling method was used to enroll a total of 405 under-fives. Structured questionnaire was used to collect data. Kato-Katz technique was used to examine stool specimens for Ascaris lumbricoides, Trichuris trichiura and hookworm spp. The Z-score for stunting, wasting and underweight were computed using the World Health Organization anthroprocedures. **Results:** The respective prevalence of soil-transmitted helminths infection and malnutrition was 67.4% (273) and 54.2% (219). Ascaris lumbricoides was the predominant helminth parasite with a prevalence of 90%, followed by T. trichiura (12%) and hookworm spp. (5%). STHs infection was significantly associated with under-nutrition (AOR: 1.88, CI 1.22-2.90) and internal displacement (AOR: 3.08, CI 1.17-8.09). Infection with A. lumbricoides was associated with both stunting and wasting (AOR: 3.04, CI 1.48-6.26) and (AOR: 3.51, CI 1.79-6.91), respectively. **Conclusions:** Both soil-transmitted helminths and malnutrition were important public health problems among under-fives in the present conflict affected areas. Internal displacement, unimproved water, absence of latrine and sanitary services were among significant determinants for STH infections.

Application of multiplex amplicon deep-sequencing (MAD-seq) to screen for putative drug resistance markers in the Necator americanus isotype-1 β-tubulin gene.

George, S., Suwondo, P., Akorli, J., Otchere, J., Harrison, L., Bilguvar, K., Knight, J., Humphries, D., Wilson, M., Caccone, A., Cappello, M.
06-07-2022
Sci Rep
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Global control of hookworm infections relies on periodic Mass Drug Administration of benzimidazole drugs to high-risk groups, regardless of infection status. Mutations in the isotype-1 β-tubulin gene have been identified in veterinary nematodes, resulting in structural changes and reduced drug-binding. In Ghana, previous studies have demonstrated significant variability in albendazole effectiveness among people infected with the hookworm Necator americanus, although the mechanisms underlying deworming response have not been defined. Using hookworm egg samples from a cross-sectional study in Ghana, we developed a multiplex amplicon deep sequencing (MAD-seq) method to screen genomic regions encapsulating putative drug-resistance markers in N. americanus isotype-1 β-tubulin gene. Three single nucleotide polymorphisms (SNPs) corresponding to resistance-associated mutations (F167Y, E198A, F200Y) within the coding region of the isotype-1 β-tubulin gene were characterized using MAD-seq in 30 matched pre- and post-treatment samples from individuals with persistent infection following therapy. Post-sequence analysis showed that the highest mean alternative nucleotide allele at each PCR amplicon was 0.034% (167amplicon) and 0.025% (198/200amplicon), suggesting minimal allelic variation. No samples contained the F167Y SNP, while one contained low-frequency reads associated with E198A (3.15%) and F200Y (3.13%). This MAD-seq method provides a highly sensitive tool to monitor the three putative benzimidazole resistance markers at individual and community levels. Further work is required to understand the association of these polymorphisms to treatment response.

Prevalence of malaria and helminth infections in rural communities in northern Sierra Leone, a baseline study to inform Ebola vaccine study protocols.

Baiden, F., Fleck, S., Leigh, B., Ayieko, P., Tindanbil, D., Otieno, T., Lawal, B., Tehtor, M., Rogers, M., Odeny, L., Hodges, M., Sonnie, M., Samai, M., Ishola, D., Lowe, B., Watson-Jones, D., Greenwood, B.
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PLoS One
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Introduction: Recurrent parasitic infections may influence the immune response to vaccines. In the Partnership for Research on Ebola VACcinations extended follow-UP and clinical research capacity build-UP (PREVAC-UP) study being undertaken in Mambolo, northern Sierra Leone, participants are being followed up to assess the potential impact of exposure to malaria and/or helminth infections on long-term immune response to two Ebola vaccines. To support the development of the assays that will be used in this evaluation, a parasitological survey was conducted in Mambolo between November 2019 and February 2020. **Methods:** Healthy individuals aged ≥1 year who were resident in Mambolo Chiefdom were selected using a stratified sampling approach and questionnaires were administered to explore their sociodemographic characteristics. Microscopy was used to detect malaria parasites, intestinal helminths and urinary schistosome infections. Rapid blood tests were used to detect infections with Onchocerca volvulus and Wuchereria bancrofti. We estimated the overall prevalence of these infections and used adjusted logistic regression models to explore risk factors for malaria and hookworm infection. **Results:** Eight hundred and fifteen (815) residents, 50.9% of whom were female were surveyed. Overall, 309 (39.1%) of 791 persons tested for malaria had a positive blood slide; Plasmodium falciparum was the dominant species. Helminth infection was detected in 122 (15.0%) of 815 stool samples including three mixed infections. The helminth infections comprised 102 (12.5%) cases of hookworm, 11 (1.3%) cases of Trichuris trichiura, 10 (1.2%) cases of Schistosoma mansoni and two (0.2%) cases of Ascaris lumbricoides. Being male (OR = 2.01, 95% CI 1.15-3.50) and residing in a non-riverine community (OR = 4.02, 95%CI 2.32-6.98) were the factors associated with hookworm infection. Onchocerca volvulus and Wuchereria bancrofti infections were found in 3.3% and 0.4% of participants respectively. **Conclusion:** Malaria and hookworm are the most prevalent parasite infections and those most likely to influence long-term immune response to Ebola vaccines among the trial participants.

GALE

Can we increase the success of scabies treatment? The effect of removing tunnels from patients in the success of scabies treatment.

Yürekli, A., Botsali, A.
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Dermatol Ther
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Recently, there has been an increase in scabies infestations. Moreover, the number of patients who do not benefit from conventional treatment regimens is increasing rapidly worldwide. This situation leads clinicians to seek new treatments. To evaluate the contribution of mechanical parasite removal to treatment success when applied prior to topical permethrin 5% treatment. The mechanical removal process was applied once during diagnosis. Two groups of 30 people each were included in the study. Permethrin treatment was given directly to the first group without any procedure. In the second group, the maximum number of tunnels that could be detected were removed from patients. After this procedure, the group received permethrin treatment. All patients were called for control after 10 days, and treatment response rates were evaluated. Sixteen (53.3%) patients who received permethrin treatment directly without any procedure responded to the treatment. In the remaining 14 (46.6%) patients, tunnels and Sarcoptes mites were still present. In the second group, which underwent tunnel removal, complete recovery was observed in 26 (86.6%) patients. The patients who did not benefit from the treatment in the study group had relatively less tunnel removal from their bodies. Removing the tunnel from the patient before the treatment increases the success of the treatment. Considering that there are 8-10 parasites on average in scabies patients, it has been determined that the tunnel removal method is not difficult and contributes to therapeutic success.

Spinosad topical suspension (0.9%): a new topical treatment for scabies.

Fernando, D., Fischer, K.
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Expert Rev Anti Infect Ther
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Introduction: Scabies is a highly contagious skin disease caused by the parasitic mite *Sarcoptes scabiei*. There is no vaccine and for the past 30 years, the first line treatments have been topical permethrin and oral ivermectin. These drugs target mainly the parasite nervous system, killing only the motile stages. As they lack ovicidal activities, repeat treatments are required to achieve complete cure. Incompliance to repeat treatments causing prolonged drug usage, has contributed to emerging drug resistances. In addition, they are not appropriate for all patient categories, specifically for infants and young children or pregnant and breast feeding women. Consequently, new single dose scabicides are urgently needed. **Areas covered:** In 2021, spinosad, a drug previously used to treat head lice, was approved by the US FDA as a topical scabies treatment. Here the pharmacology, clinical efficacy and tolerability of this drug are discussed. **Expert opinion:** As the first single dose scabicide the formulated 0.9% topical Spinosad solution shows significant efficacy, little systemic absorption and no serious adverse reactions, making it a promising treatment for classical scabies in patients older than four years.

Tropical Parasitic Itch in Returned Travelers and Immigrants from Endemic Areas.

Revue de littérature

Ju, T., Vander Does, A., Ingrasci, G., Norton, S., Yosipovitch, G.

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J Eur Acad Dermatol Venereol
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Itch is the most common skin symptom among tropical parasitic diseases (TPD) but there are limited data about its characteristics in these conditions. In dermatology practices and travelers' health clinics in the developed world, itch is a common complaint among travelers returning from endemic areas, as well among migrants arriving from endemic areas, where they may have been exposed to TPD. Studying aspects of pruritus among TPD may lead to improvements in prompt, accurate diagnosis and management of these conditions. This review examines the major itch-inducing TPDs, including schistosomiasis, echinococcosis, onchocerciasis, scabies, cutaneous larva migrans, larva currens, African trypanosomiasis, dracunculiasis, and other causes of travel associated pruritus. We focus on the link between pruritus and other symptoms, etiology, clinical staging, and therapy options for these parasitic illnesses. Because some tropical parasitic diseases can present with significant pruritus, we attempt to identify aspects of the pruritus that are characteristic of-or unique to-specific conditions. These diagnostic insights may help clinicians create a rational and focused differential diagnosis and help determine optimal disease management pathways. In this sense, management involves treating the individual, seeking epidemiologically linked cases, preventing recurrences or relapses, and reducing spread of the disease.

MORSURES DE SERPENT

Biotechnological interventions and indole alkaloid production in Rauvolfia serpentina.

Revue de littérature

Dey, A., Roy, D., Mohture, V., Ghorai, M., Rahman, M., Anand, U., Dewanjee, S., Radha, ., Kumar, M., Prasanth, D., Jha, N., Jha, S., Shekhawat, M., Pandey, D.
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Appl Microbiol Biotechnol
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Rauvolfia serpentina (L). Benth. ex Kurz. (Apocynaceae), commonly known as Sarpagandha or Indian snakeroot, has long been used in the traditional treatment of snakebites, hypertension, and mental illness. The plant is known to produce an array of indole alkaloids such as reserpine, ajmaline, amalicine, etc. which show immense pharmacological and biomedical significance. However, owing to its poor seed viability, lesser germination rate and overexploitation for several decades for its commercially important bioactive constituents, the plant has become endangered in its natural habitat. The present review comprehensively encompasses the various biotechnological tools employed in this endangered Ayurvedic plant for its in vitro propagation, role of plant growth regulators and additives in direct and indirect regeneration, somatic embryogenesis and synthetic seed production, secondary metabolite production in vitro, and assessment of clonal fidelity using molecular markers and genetic transformation. In addition, elicitation and other methods of optimization of its indole-alkaloids are also described herewith. KEY POINTS: • Latest literature on in vitro propagation of Rauvolfia serpentina • Biotechnological production and optimization of indole alkaloids • Clonal fidelity and transgenic studies in R. serpentina.

"Then they prayed, they did nothing else, they just prayed for the boy and he was well": A qualitative investigation into the perceptions and behaviours surrounding snakebite and its management in rural communities of Kitui county, Kenya.

Wood, L., Ngari, C., Parkito, S., Barnes, K., Otundo, D., Misiani, D., Kepah, G., Trelfa, A., Olouch, G., Harrison, R., Tianyi, F.
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PLoS Negl Trop Dis
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Introduction: Human-snake interactions are common in tropical regions where subsistence-farming and livestock-herding activities predominate alongside proliferation of snakes. Local beliefs and perceptions about snakes and snakebites influence human behaviour. Understanding these beliefs and perceptions can inform the development of resources to drive behaviour changes and to minimise the risk of injury to both humans and snakes. This qualitative study, conducted between May and July 2019, sought to explore the beliefs and perceptions regarding snakes and snakebites, and methods of prevention and management among members of the community in Kitui County, Kenya. Methods: Semi-structured interviews were used to collect qualitative data from 23 participants, recruited using a stratified purposeful sampling strategy in four selected sub-counties of Kitui county. Interview data was anonymised and coded and a thematic analysis was conducted using NVivo 12. Results: People from Kitui county mostly had negative perceptions about snakes. There was a generalised awareness of the need to prevent snakebite, predominantly through keeping snakes away from homes/compounds. However, implementation was limited by financial constraints. Participants also identified logistic and financial obstacles to early hospital presentation following a snakebite, and they expressed a strong preference of having their snakebites treated in a hospital over consulting traditional healers. There was a universal recognition of the benefit of early intervention with a specific appreciation of the utility of the black stone. Furthermore, the removal of a snake's "teeth" was an expected treatment outcome for some community members, with the failure to do so perceived as causing poor wound healing or persistence of symptoms. Some religious groups held views which differed from most participants. Conclusion: There is a need to explore and clarify common misconceptions about snakes and first aid treatment of snakebites, encourage learning about the true nature of

snakes, and highlight beneficial uses of snakes. A change in the epistemological conception of community education material by enhancing the value and use of local forms of knowledge, and the employment of art techniques to transmit this knowledge, could improve community perception and methods of snakebite prevention. Patient expectations should be appropriately managed by discussing possible outcomes, incorporating follow-up visits and addressing long-term complications of snakebites.