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DENGUE, CHIKUNGUNYA ET MALADIE A VIRUS ZIKA

Health needs of mothers of children with Congenital Zika Syndrome: an integrative review.

Vale, P., Araújo, P., Cardoso, S., Santos Junior, H., Carvalho, R., Carvalho, E.
22-04-2022
Rev Bras Enferm
https://pubmed.ncbi.nlm.nih.gov/35476097

Objectives: to evidence and analyze the health needs of mothers of children with Congenital Zika Syndrome. Methods: a total of 44 articles published between October/2015 and March/2021 on PubMed, LILACS, Scopus, Web of Science and Science Direct were included. The RTI bank and CASP score were applied to classify the methodological quality of the studies. Reflective content analysis and Cecílio and Matsumoto's taxonomy were used for analysis. Visual map was used as a technique for presenting the results. Results: mothers need access to social protection, family-centered, multi-professional empathetic monitoring, cultivating bonds and affection by professionals, sharing of care between health network services, strengthening the social support network and fostering coexistence groups between them. Final considerations: intersectoral initiatives must be implemented for better housing conditions, fighting stigma, holding parents accountable and resuming life project.

Molecular aspects of Chikungunya virus infections in cancer patients.

Familiar-Macedo, D., Gama, B., Emmel, V., Vera-Lozada, G., Abdelhay, E., Martins, I., Hassan, R.
22-04-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35475905

Background: Chikungunya virus (CHIKV) is an arbovirus that can cause chronic and debilitating manifestations. The first autochthonous case in Rio de Janeiro state was diagnosed in 2015, and an outbreak was declared in 2016. Objective: The aim of this work was to evaluate CHIKV viral load in serum, plasma and urine in cancer patients to determine the best sample for diagnosis, as well as perform molecular characterisation and phylogenetic analysis of circulating strains. Methods: Paired serum, plasma and urine collected from 31 cancer patients were tested by real-time quantitative polymerase chain reaction (qPCR) and a segment of the CHIKV E1 gene was sequenced. Findings: We detected 11 CHIKV+ oncological patients. Paired samples analyses of nine patients showed a different pattern of detection. Also, a higher viral load in plasma (6.84 log10) and serum (6.07 log10) vs urine (3.76 log10) was found. Phylogenetic analysis and molecular characterisation revealed East/Central/Southern Africa (ECSA) genotype circulation and three amino acids substitutions (E1-K211T, E1-M269V, E1-T288I) in positive patients. Main conclusion: The results indicate the bioequivalence of serum and plasma for CHIKV diagnosis, with urine being an important complement. ECSA genotype was circulating among patients in the period of the 2016 outbreak with K211T, M269V and T288I substitution.

Rotational thromboelastometry in critical phase of dengue infection: Association with bleeding.

Wickramasinghe, W., Alvitigala, B., Perera, T., Karunanayake, P., Jayasinghe, S., Rajapakse, S., Weeratunga, P., Wijewickrama, A., Arya, R., Goerlinger, K., Gooneratne, L.
22-04-2022
Res Pract Thromb Haemost
https://doi.org/10.1002/rth2.12704

Background: The critical phase of dengue carries a high risk of bleeding. Associations of coagulation test parameters and the risk of bleeding in the critical phase is unclear. This study examines the association of rotational thromboelastometry (ROTEM *delta* and ROTEM *platelet*) with bleeding risk of patients with dengue in the critical phase. Methods: A total of 105 patients with confirmed dengue in the critical phase were recruited, with two subsequent prospective time point analyses of ROTEM parameters and platelet count within 24 and 48 hours from the onset of the critical phase. Conventional coagulation tests were performed only at the initial time point. Results: Twenty of 105 patients developed bleeding after onset of the critical phase. Within the first 24 hours of critical-phase onset, platelet count, coagulation tests, and ROTEM *delta* were unable to differentiate patients with bleeding manifestations from those without ($P < .05$). Area under the curve of thrombin receptor activating peptide-6 assay of ROTEM *platelet* (TRAPTEM) discriminated patients with bleeding manifestations from those without, at a cutoff value of <12.5 Ω*min at a sensitivity and specificity of 73.7%, and 60.2%. In patients who developed bleeding, the maximum lysis of extrinsic pathway of ROTEM was significantly lower in patients with severe bleeding compared to those with mild to moderate bleeding. ($4.3 \pm 3.4\%$ vs $9.4 \pm 7.5\%$; $P = .01$). Conclusion: An association with bleeding manifestations and TRAPTEM suggest a potential role for defective platelet aggregation in the pathogenesis of bleeding in the critical phase of dengue.

Unequal burden of zika-associated microcephaly among populations with public and private healthcare in Salvador, Brazil.

Aromolaran, A., Araujo, K., Ladines-Lim, J., Nery, N., do Rosário, M., Rastely, V., Archanjo, G., Daltro, D., Carvalho, G., Pimentel, K., de Almeida, J., de Siqueira, I., Ribeiro, H., Oliveira-Filho, J., de Oliveira, D., Henriques, D., Rodrigues, S., Vasconcelos, P., de Almeida, A., Sacramento, G., Cruz, J., Sarno, M., Freitas, B., Mattos, A., Khouri, R., Reis, M., Ko, A., Costa, F.
22-04-2022
Int J Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35470025

Objective: To describe the differences in clinical presentation and relative disease burden of Congenital Zika Syndrome (CZS)

associated microcephaly at two large hospitals in Salvador, Brazil that serve patients of different socioeconomic status (SES). **Methods:** Clinical and serologic data were collected prospectively from pregnant women, and their infants, who delivered at two study centers during the 2015-2016 Zika virus epidemic in Salvador, Brazil. **Results:** Pregnant women from Salvador, Brazil delivering in a low SES hospital had three times higher ZIKV exposure rate compared to women at a high SES hospital. However, different SES hospitals had similar prevalence of infants with CZS associated microcephaly (10% vs 6%, p=0.16) after controlling for ZIKV exposure in their mothers. **Conclusions:** Our study supports the positive association between low SES, high maternal ZIKV exposure and high rates of CZS associated microcephaly.

Temperate Conditions Limit Zika Virus Genome Replication.

Tesla, B., Powers, J., Barnes, Y., Lakhani, S., Acciani, M., Brindley, M.
25-04-2022
J Virol
https://doi.org/10.1128/jvi.00165-22

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

Detecting space-time patterns of disease risk under dynamic background population.

Hohl, A., Tang, W., Casas, I., Shi, X., Delmelle, E.
20-04-2022
J Geogr Syst
https://doi.org/10.1007/s10109-022-00377-7

We are able to collect vast quantities of spatiotemporal data due to recent technological advances. Exploratory space-time data analysis approaches can facilitate the detection of patterns and formation of hypotheses about their driving processes. However, geographic patterns of social phenomena like crime or disease are driven by the underlying population. This research aims for incorporating temporal population dynamics into spatial analysis, a key omission of previous methods. As population data are becoming available at finer spatial and temporal granularity, we are increasingly able to capture the dynamic patterns of human activity. In this paper, we modify the space-time kernel density estimation method by accounting for spatially and temporally dynamic background populations (ST-DB), assess the benefits of considering the temporal dimension and finally, compare ST-DB to its purely spatial counterpart. We delineate clusters and compare them, as well as their significance, across multiple parameter configurations. We apply ST-DB to an outbreak of dengue fever in Cali, Colombia during 2010-2011. Our results show that incorporating the temporal dimension improves our ability to delineate significant clusters. This study addresses an urgent need in the spatiotemporal analysis literature by using population data at high spatial and temporal resolutions.

Design of an Epitope-Based Peptide Vaccine Against Dengue Virus Isolate from Eastern Uttar Pradesh, India.

Gupta, S., Kumar, A.
18-04-2022
Int J Pept Res Ther
https://doi.org/10.1007/s10989-022-10402-4

Dengue outbreaks are a serious public health concern that occurs on a regular basis in various locations of India. According to the Government of India's National Center for Vector-Borne Disease Control, a total of 1,23,106 dengue cases were identified in India as of October 2021. The currently available dengue vaccine was found to be ineffective

against all serotypes of the virus. Dengue virus serotype 2 was reported to be the sole predominant serotype in Eastern Uttar Pradesh, India. An epitope-based peptide vaccine is believed to be safe and effective against all serotypes of the dengue virus. In this work, an epitope-based peptide vaccine based on envelope protein against the dengue virus was developed using the reverse vaccinology method. T-cell epitopes present in the envelope protein were screened using different immunoinformatic tools. Epitopes predicted by all servers were chosen and additionally picked out on the grounds of their antigenic reactivity, immunogenicity, toxicity, and allergenicity assessment. Three potent T cell epitopes as IVQPENLEY, ILIGVVITW, and DTAWDFGSL were screened, which binds with HLA-B*35:01, HLA-B*58:01, HLA-A*26:01 alleles, respectively. To build a 3D structure model of epitopes and alleles, the PepstrMod and Swiss-Model servers were used. Predicted epitopes and HLA alleles were docked using the HPEPDOCK server to confirm binding ability. These anticipated epitopes were found to cover the greatest number of populations in India and around the world. These identified epitopes have a high potential for eliciting an immune response in the development of a vaccine against the dengue virus, while further experimental validation is required for final confirmation. The online version contains supplementary material available at 10.1007/s10989-022-10402-4.

Zika virus-induced TNF-α signaling dysregulates expression of neurologic genes associated with psychiatric disorders.

Kung, P., Chou, T., Lindman, M., Chang, N., Estevez, I., Buckley, B., Atkins, C., Daniels, B.
24-04-2022
J Neuroinflammation
https://doi.org/10.1186/s12974-022-02460-8

Background: Zika virus (ZIKV) is an emerging flavivirus of global concern. ZIKV infection of the central nervous system has been linked to a variety of clinical syndromes, including microcephaly in fetuses and rare but serious neurologic disease in adults. However, the potential for ZIKV to influence brain physiology and host behavior following apparently mild or subclinical infection is less well understood. Furthermore, though deficits in cognitive function are well-documented after recovery from neuroinvasive viral infection, the potential impact of ZIKV on other host behavioral domains has not been thoroughly explored. Methods: We used transcriptomic profiling, including unbiased gene ontology enrichment analysis, to assess the impact of ZIKV infection on gene expression in primary cortical neuron cultures. These studies were extended with molecular biological analysis of gene expression and inflammatory cytokine signaling. In vitro observations were further confirmed using established in vivo models of ZIKV infection in immunocompetent hosts. Results: Transcriptomic profiling of primary neuron cultures following ZIKV infection revealed altered expression of key genes associated with major psychiatric disorders, such as bipolar disorder and schizophrenia. Gene ontology enrichment analysis also revealed significant changes in gene expression associated with fundamental neurobiological processes, including neuronal development, neurotransmission, and others. These alterations to neurologic gene expression were also observed in the brain in vivo using several immunocompetent mouse models of ZIKV infection. Mechanistic studies identified TNF-α signaling via TNFR1 as a major regulatory mechanism controlling ZIKV-induced changes to neurologic gene expression. Conclusions: Our studies reveal that cell-intrinsic innate immune responses to ZIKV infection profoundly shape neuronal transcriptional profiles, highlighting the need to further explore associations between ZIKV infection and disordered host behavioral states.

A barcoding pipeline for mosquito surveillance in Nepal, a biodiverse dengue-endemic country.

Hartke, J., Reuss, F., Kramer, I., Magdeburg, A., Deblauwe, I., Tuladhar, R., Gautam, I., Dhimal, M., Müller, R.
24-04-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05255-1

Background: Vector-borne diseases are on the rise on a global scale, which is anticipated to further accelerate because of anthropogenic climate change. Resource-limited regions are especially hard hit by this increment with the currently implemented surveillance programs being inadequate for the observed expansion of potential vector species. Cost-effective methods that can be easily implemented in resource-limited settings, e.g. under field conditions, are thus urgently needed to function as an early warning system for vector-borne disease epidemics. Our aim was to enhance entomological capacity in Nepal, a country with endemicity of numerous vector-borne diseases and with frequent outbreaks of dengue fever. Methods: We used a field barcoding pipeline based on DNA nanopore sequencing (Oxford Nanopore Technologies) and verified its use for different mosquito life stages and storage methods. We furthermore hosted an online workshop to facilitate knowledge transfer to Nepalese scientific experts from different disciplines. Results: The use of the barcoding pipeline could be verified for adult mosquitos and eggs, as well as for homogenized samples, dried specimens, samples that were stored in ethanol and frozen tissue. The transfer of knowledge was successful, as reflected by feedback from the participants and their wish to implement the method. Conclusions: Cost effective strategies are urgently needed to assess the likelihood of disease outbreaks. We were able to show that field sequencing provides a solution that is cost-effective, undemanding in its implementation and easy to learn. The knowledge transfer to Nepalese scientific experts from different disciplines provides an opportunity for sustainable implementation of low-cost portable sequencing solutions in Nepal.

Designing vaccine candidates against dengue virus by in silico studies on structural and nonstructural domains.

Shoushtari, M., Mafakher, L., Rahmati, S., Salehi-Vaziri, M.,

Arashkia, A., Roohvand, F., Teimoori-Toolabi, L., Azadmanesh, K.
21-04-2022
Mol Cell Probes
https://pubmed.ncbi.nlm.nih.gov/35461964

One-third of the world's population is at risk of Dengue infection. Envelope domain 3 (EDIII) and nonstructural protein1 (NS1) proteins as the potent antigenicity regions for humoral immunity in addition to the bc loop region as a completely conserved region have been used for designing protective vaccines. We aimed to design vaccine candidates according to the bc loop, EDIII, and NS1 regions of Dengue serotype2 to be used as vaccine candidates for all serotypes of Dengue virus especially serotype 2. Firstly the bc loop region with EDII fragments at both ends as well as EDIII and NS1 regions were used which were linked with the GGGGS linker to the bc loop region. In two other strategies, the bc loop with EDII and NS1 fragments at both ends was used to increase its structural stability. Tertiary structure prediction and validation of vaccine constructs indicated that all vaccine constructs were modeled with high quality and stable structure during molecular dynamics simulation. B cell epitope mapping by Bepipred and ElliPro methods confirmed the existence of high potent epitopes in the bc loop, EDIII, and NS1 regions in both linear and conformational B cell epitopes. Furthermore, molecular docking for the bc loop region demonstrated that all designed vaccines have a higher affinity to interact with 1C19 monoclonal antibody than only the bc loop region or bc loop epitope in the protein EII. Our data of in silico studies indicated that the designed vaccines could effectively induce humoral immunity against four dengue serotypes.

Nafamostat mesylate as a broad-spectrum candidate for the treatment of flavivirus infections by targeting envelope proteins.

Yan, Y., Yang, J., Xiao, D., Yin, J., Song, M., Xu, Y., Zhao, L., Dai, Q., Li, Y., Wang, C., Wang, Z., Ren, X., Yang, X., Ni, J., Liu, M., Guo, X., Li, W., Chen, X., Liu, Z., Cao, R., Zhong, W.
20-04-2022
Antiviral Res
https://pubmed.ncbi.nlm.nih.gov/35460703

Epidemics caused by flaviviruses occur globally; however, no antiviral drugs treating flaviviruses infections have yet been developed. Nafamostat (NM) is a protease inhibitor approved for pancreatitis and anti-coagulation. The anti-flavivirus potential of NM has yet to be determined. Here, utilizing in vitro and in vivo infection assays, we present that NM effectively inhibits Zika virus (ZIKV) and other flaviviruses in vitro. NM inhibited the production of ZIKV viral RNA and proteins originating from Asia and African lineage in human-, mouse- and monkey-derived cell lines and the in vivo anti-ZIKV efficacy of NM was verified. Mode-of-action analysis using time-of-drug-addition assay, infectivity inhibition assay, surface plasmon resonance assay, and molecular docking revealed that NM interacted with viral particles and blocked the early stage of infection by targeting the domain III of ZIKV envelope protein. Analysing the anti-flavivirus effects of NM-related compounds suggested that the antiviral effect depended on the unique structure of NM. These findings suggest the potential use of NM as an anti-flavivirus candidate, and a novel drug design approach targeting the flavivirus envelope protein.

Early infection of Zika virus in the male reproductive system of AG129 mice: molecular and immunohistochemical evaluation.

Lima, M., Cabral, Á., Bittar, C., Falleiros Junior, L., Guerra, L., Carneiro, B., de Souza Ferreira, L., Nogueira, M., Taboga, S., Calmon, M., Rahal, P.
23-04-2022
Braz J Microbiol
https://doi.org/10.1007/s42770-022-00761-x

Sexual transmission of Zika virus (ZIKV), an important arbovirus, and the virus persistence in semen raise several questions about how and where it circulates in the male reproductive system (MRS). Several studies reported detection of the virus in testes, epididymis, and prostate at 5 days post-infection (dpi) or more in animal models. In the present study, we investigated the interactions of ZIKV with mouse MRS using the AG129 strain, a ZIKV permissive immunodeficient mouse strain, at two dpi. Viral RNA was detected in blood, testes, epididymis, and prostatic complexes (prostate and seminal vesicles). Immunohistochemical (IHC) analyses, based on the envelope protein, showed an early infection in organs of MRS since ZIKV positive antigens were detected in cells within or surrounding blood vessels, Sertoli, and germ cells in testes and epithelial cells in epididymis and prostate. Positive antigens for NS5 protein, the virus RNA-dependent RNA polymerase, were also detected by IHC in these organs and circulating leukocytes, suggesting that the virus replicates in these sites as early as 2 days post-infection. Analysis of the early stages of ZIKV infection in MRS may improve the current knowledge about this issue and contribute to the development of therapies directed to the infection at this site.

Immunological implications of diverse production approaches for Chikungunya virus-like particle vaccines.

Revue de littérature

Thompson, D., Metz, S., Abad, C., Beaty, S., Warfield, K.
19-04-2022
Vaccine
https://pubmed.ncbi.nlm.nih.gov/35459557

Chikungunya virus (CHIKV), an arbovirus from the Alphavirus genus, causes sporadic outbreaks and epidemics and can cause acute febrile illness accompanied by severe long-term arthralgias. Over 20 CHIKV vaccine candidates have been developed over the last two decades, utilizing a wide range of vaccine platforms, including virus-like particles (VLP). A CHIKV VLP vaccine candidate is among three candidates in late-stage clinical testing and has potentially promising data in

nonclinical and clinical studies exploring safety and vaccine immunogenicity. Despite the consistency of the CHIKV VLP structure, vaccine candidates vary significantly in protein sequence identity, structural protein expression cassettes and their mode of production. Here, we explore the impact of CHIKV VLP coding sequence variation and the chosen expression platform, which affect VLP expression yields, antigenicity and overall vaccine immunogenicity. Additionally, we explore the potential of the CHIKV VLP platform to be modified to elicit protection against other pathogens.

The cargo adaptor protein CLINT1 is phosphorylated by the Numb-associated kinase BIKE and mediates dengue virus infection.

Schor, S., Pu, S., Nicolaescu, V., Azari, S., Kõivomägi, M., Karim, M., Cassonnet, P., Saul, S., Neveu, G., Yueh, A., Demeret, C., Skotheim, J., Jacob, Y., Randall, G., Einav, S.
19-04-2022
J Biol Chem
https://pubmed.ncbi.nlm.nih.gov/35452674

The signaling pathways and cellular functions regulated by the four Numb-associated kinases (NAKs) are largely unknown. We previously reported that AAK1 and GAK control intracellular trafficking of RNA viruses, and recently revealed a requirement for BIKE in early and late stages of dengue virus (DENV) infection. However, the downstream targets phosphorylated by BIKE in this process have not yet been identified. Here, to identify BIKE substrates, we conducted a barcode fusion genetics-yeast two-hybrid screen and retrieved publicly available data generated via affinity-purification mass spectrometry. We subsequently validated 19 of 47 putative BIKE interactors using mammalian cell-based protein-protein interaction assays. We found that CLINT1, a cargo-specific adaptor implicated in bidirectional Golgi-to-endosome trafficking, emerged as a predominant hit in both screens. Our experiments indicated that BIKE catalyzes phosphorylation of a threonine 294 (T294) CLINT1 residue both in vitro and in cell culture. Our findings revealed that CLINT1 phosphorylation mediates its binding to the DENV nonstructural 3 protein and subsequently promotes DENV assembly and egress. In addition, using live-cell imaging we revealed that CLINT1 cotraffics with DENV particles and is involved in mediating BIKE's role in DENV infection. Finally, our data suggest that additional cellular BIKE interactors implicated in the host immune and stress responses and the ubiquitin proteasome system might also be candidate phosphorylation substrates of BIKE. In conclusion, these findings reveal cellular substrates and pathways regulated by the understudied NAK enzyme BIKE, a mechanism for CLINT1 regulation, and control of DENV infection via BIKE signaling, with potential implications for cell biology, virology, and host-targeted antiviral design.

Monocytes and macrophages in pregnancy: The good, the bad, and the ugly.

Revue de littérature

True, H., Blanton, M., Sureshchandra, S., Messaoudi, I.
21-04-2022
Immunol Rev
https://doi.org/10.1111/imr.13080

A successful human pregnancy requires precisely timed adaptations by the maternal immune system to support fetal growth while simultaneously protecting mother and fetus against microbial challenges. The first trimester of pregnancy is characterized by a robust increase in innate immune activity that promotes successful implantation of the blastocyst and placental development. Moreover, early pregnancy is also a state of increased vulnerability to vertically transmitted pathogens notably, human immunodeficiency virus (HIV), Zika virus (ZIKV), SARS-CoV-2, and Listeria monocytogenes. As gestation progresses, the second trimester is marked by the establishment of an immunosuppressive environment that promotes fetal tolerance and growth while preventing preterm birth, spontaneous abortion, and other gestational complications. Finally, the period leading up to labor and parturition is characterized by the reinstatement of an inflammatory milieu triggering childbirth. These dynamic waves of carefully orchestrated changes have been dubbed the "immune clock of pregnancy." Monocytes in maternal circulation and tissue-resident macrophages at the maternal-fetal interface play a critical role in this delicate balance. This review will summarize the current data describing the longitudinal changes in the phenotype and function of monocyte and macrophage populations in healthy and complicated pregnancies.

Data-driven computational intelligence applied to dengue outbreak forecasting: a case study at the scale of the city of Natal, RN-Brazil.

Sanchez-Gendriz, I., de Souza, G., de Andrade, I., Neto, A., de Medeiros Tavares, A., Barros, D., de Morais, A., Galvão-Lima, L., de Medeiros Valentim, R.
21-04-2022
Sci Rep
https://doi.org/10.1038/s41598-022-10512-5

Dengue is recognized as a health problem that causes significant socioeconomic impacts throughout the world, affecting millions of people each year. A commonly used method for monitoring the dengue vector is to count the eggs that Aedes aegypti mosquitoes have laid in spatially distributed ovitraps. Given this approach, the present study uses a database collected from 397 ovitraps allocated across the city of Natal, RN-Brazil. The Egg Density Index for each neighborhood was computed weekly, over four complete years (from 2016 to 2019), and simultaneously analyzed with the dengue case incidence. Our results illustrate that the incidence of dengue is related to the socioeconomic level of the neighborhoods in the city of Natal. A deep learning algorithm was used to predict future dengue case incidence, either based on the previous weeks of dengue incidence or the number of eggs present in the ovitraps. The analysis reveals that ovitrap data allows earlier prediction (four to six weeks) compared to dengue incidence itself (one week).

Therefore, the results validate that the quantification of Aedes aegypti eggs can be valuable for the early planning of public health interventions.

Prohemocytes are the main cells infected by dengue virus in Aedes aegypti and Aedes albopictus.

Cheng, L., Liu, W., Su, M., Huang, S., Wang, J., Chen, C.
21-04-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05276-w

Background: The primary disease vectors for dengue virus (DENV) transmission between humans are the mosquitoes Aedes aegypti and Aedes albopictus, with Ae. aegypti population size strongly correlated with DENV outbreaks. When a mosquito is infected with DENV, the virus migrates from the midgut to the salivary glands to complete the transmission cycle. How the virus crosses the hemocoel, resulting in systemic infection, is still unclear however. During viral infection and migration, the innate immune system is activated in defense. As part of cellular-mediated immunity, hemocytes are known to defend against bacteria and Plasmodium infection and may also participate in defending against DENV infection. Hemocytes are categorized into three cell types: prohemocytes, granulocytes, and oenocytoids. Here, we investigated which hemocytes can be infected by DENV and compare hemocyte infection between Ae. aegypti and Ae. albopictus. Methods: Hemocytes were collected from Ae. aegypti and Ae. albopictus mosquitoes that were intrathoracically infected with DENV2-GFP. The collected hemocytes were then identified via Giemsa staining and examined microscopically for morphological differences and viral infection. Results: All three types of hemocytes were infected by DENV, though the predominantly infected cell type was prohemocytes. In Ae. aegypti, the highest and lowest infection rates at 7 days post infection occurred in prohemocytes and granulocytes, respectively. Prohemocytes were also the primary infection target of DENV in Ae. albopictus, with similar infection rates across the other two hemocyte groups. The ratios of hemocyte composition did not differ significantly between non-infected and infected mosquitoes for either species. Conclusions: In this study, we showed that prohemocytes were the major type of hemocyte infected by DENV in both Ae. aegypti and Ae. albopictus. The infection rate of prohemocytes in Ae. albopictus was lower than that in Ae. aegypti, which may explain why systemic DENV infection in Ae. albopictus is less efficient than in Ae. aegypti and why Ae. albopictus is less correlated to dengue fever outbreaks. Future work in understanding the mechanisms behind these phenomena may help reduce arbovirus infection prevalence.

Incidence of dengue fever in Israeli travelers 2008-2019.

Meltzer, E., Sharon, A., Lustig, Y., Schwartz, E.
18-04-2022
Travel Med Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35447321

Background: Dengue virus (DENV) is a frequent travel-related infection, but longitudinal data on its incidence is limited. We aimed to study temporal trends of travel-related DENV burden and its geographical sources. Methods: All cases of laboratory-confirmed DENV infection diagnosed at the Central Virology Laboratory of the Israeli Ministry of Health during 2008-2019 were evaluated. Numbers of Israeli tourist-entries to DENV endemic countries were available from the UN World Tourist Organization (UNWTO) database. DENV attack rates were calculated as cases per 100,000 traveler-entries. In addition, for Thailand and India incidence rates were calculated, using the average duration of stay reported in diagnosed DENV cases. Results: During 2008-2019, 425 Israeli travelers were diagnosed with DENV: 80.3%, 12.8% and 6.9% were acquired in Asia, America and Africa respectively. The average global DENV attack rate increased from 2.5 cases per 100,000 tourist-entries in 2008 to 10.7 cases per 100,000 tourist-entries in 2019. Region-specific DENV attack rates were 4.4, 3.2 and 2.1 cases per 100,000 tourist-entries to Asia, Africa, and America respectively. The highest number of DENV cases were reported from Thailand and India; DENV incidence rates increased from 94.5 to 142.2 cases per 100,000 travel-years, and from 49.3 to 90.4 cases per 100,000 travel-years for Thailand and India respectively. Conclusion: Among Israeli travelers, worldwide DENV attack-rates have quadrupled during 2008-2019, reflecting both a growing DENV burden in Asia, but also the emergence of Africa as an important source of DENV. The need to protect travelers through vaccination remains urgent.

Bioprospection for new larvicides against Aedes aegypti based on ethnoknowledge from the Amazonian São Sebastião de Marinaú riverside community.

Correa de Oliveira, P., Barreto Sousa, J., Albernaz, L., Coelho-Ferreira, M., Salmen Espindola, L.
18-04-2022
J Ethnopharmacol
https://pubmed.ncbi.nlm.nih.gov/35447199

Ethnopharmacological relevance: Vector-borne diseases represent a huge global burden impacting health systems. Aedes aegypti is the main vector of arboviral diseases including dengue, Zika, chikungunya and urban yellow fever in both tropical and subtropical areas. Ethnopharmacological investigations provide potential avenues for developing new vector control strategies. Aim of the study: The objective of this study is to document the São Sebastião de Marinaú riverside community's ethnoknowledge of local plants used to control mosquitoes and perform bioguided fractionation to isolate the compounds active against the arboviral disease vector Ae. aegypti. Materials and methods: Semi-structured interviews were conducted with residents of the Marinaú community located in the Caxiuanã National Forest, in the Amazon biome, Pará, Brazil. The plants used to control mosquitoes were subjected to phytochemical studies guided

by Ae. aegypti assays. Extracts were obtained from seven species using distinct organic solvents. Active extracts and fractions were separated by chromatographic techniques. Isolated compounds were characterized by NMR, LC/MS and GC/MS. Sample activity against Ae. aegypti larvae and pupae was evaluated after 24, 48 and 72 h exposure. The extracts were also investigated against adult female mosquitoes. The LC_{50} values were determined by diluting each sample to obtain different concentrations in the respective activity range. **Results:** The Marinaú community uses more than ten plants as a repellent, most of which are trees native to the region. The primary applications of these plants to protect against insect bites were: burning plants (fumigation), application of body oils and bathing in macerated plants. Carapa guianensis is the predominant species used as a repellent. Extracts from Diospyros guianensis fruits, Carapa guianensis seed shells and Aspidosperma nitidum wood demonstrated Ae. aegypti larvicidal activity. The C. guianensis seed shell extract demonstrated a residual larvicidal effect. Plumbagin, stigmasterol, β-sitosterol, betulinic, ursolic and oleanolic acids, and betulin were identified in the D. guianensis extract. The plumbagin, ursolic and oleanolic acids displayed larvicidal activity. Oleanolic, ursolic and betulinic acids, and betulin were considered pupicidal. Aricine, the major alkaloid isolated from A. nitidum wood, also presented larvicidal activity. **Conclusions:** Ten plant species traditionally used by the Marinaú community to afford protection against mosquitoes were reported. C. guianensis, D. guianensis and A. nitidum extracts were considered larvicidal against Ae. aegypti. Four triterpenes stood out as very active compounds against pupae. Aricine, an indole alkaloid, displayed larvicidal activity. Therefore, traditional knowledge of Amazonian plants combined with bioguided fractionation constitutes a strategy for the development of eco-friendly insecticides to control Ae. aegypti, an arbovirus vector.

Concomitant pyroptotic and apoptotic cell death triggered in macrophages infected by Zika virus.

Wen, C., Yu, Y., Gao, C., Qi, X., Cardona, C., Xing, Z.
21-04-2022
PLoS One
https://doi.org/10.1371/journal.pone.0257408

Zika virus (ZIKV) is a positive-sense RNA flavivirus and can cause serious neurological disorders including microcephaly in infected fetuses. As a mosquito-borne arbovirus, it enters the bloodstream and replicates in various organs. During pregnancy, it can be transmitted from the blood of the viremic mother to the fetus by crossing the placental barrier. Monocytes and macrophages are considered the earliest blood cell types to be infected by ZIKV. As a first line defense, these cells are crucial components in innate immunity and host responses and may impact viral pathogenesis in humans. Previous studies have shown that ZIKV infection can activate inflammasomes and induce proinflammatory cytokines in monocytes. In this report, we showed that ZIKV could infect and induce cell death in human and murine macrophages. In addition to the presence of cleaved caspase-3, indicating that apoptosis was involved, we identified the cleaved caspase-1 and gasdermin D (GSDMD) as well as increased secretion of IL-1β and IL-18. This suggests that the inflammasome was activated and that may lead to pyroptosis in infected macrophages. The pyroptosis was NLRP3-dependent and could be suppressed in the macrophages treated with shRNA to target and knockdown caspase-1. It was also be inhibited by an inhibitor for caspase-1, indicating that the pyroptosis was triggered via a canonical approach. Our findings in this study demonstrate a concomitant occurrence of apoptosis and pyroptosis in ZIKV-infected macrophages, with two mechanisms involved in the cell death, which may have potentially significant impacts on viral pathogenesis in humans.

Social and housing indicators of dengue and chikungunya in Indian adults aged 45 and above: Analysis of a nationally representative survey (2017-18).

Paulson, W., Kodali, N., Balasubramani, K., Dixit, R., Chellappan, S., Behera, S., Balabaskaran Nina, P.
20-04-2022
Arch Public Health
https://doi.org/10.1186/s13690-022-00868-5

Background: Dengue and chikungunya (CHIKV) are the two major vector-borne diseases of serious public health concern in India. Studies on socioeconomic and housing determinants of dengue and CHIKV at a pan-India level are lacking. Here, we took advantage of the recently carried out Longitudinal Ageing Study in India (LASI) carried out across all the states and Union Territories of India to study the social indicators of dengue and CHIKV in India. **Methods:** LASI-1 (2017-2018) data on the self-reported period prevalence of dengue and CHIKV from 70,932 respondents aged ≥45 years were used for this analysis. The state-wise distribution of dengue and CHIKV was mapped. Prevalence was estimated for each study variable, and the difference was compared using the $\chi 2$ test. The adjusted odds ratios (AOR) of the socioeconomic and housing variables for dengue and CHIKV were estimated using the multiple logistic regression model. **Results:** Urban residence is the major socio-economic indicator of dengue and CHIKV (dengue AOR: 1.57, 95% CI: 1.18-2.11; CHIKV AOR: 1.84, 95% CI: 1.36-2.49). The other notable indicator is wealth; rich respondents have higher odds of dengue and CHIKV. Adults older than 54 years and those with high school education and above are associated with a lower likelihood of dengue and CHIKV. In addition, CHIKV is associated with scheduled and forward castes, households with improper toilet facilities, open defecation, and kutcha house type. **Conclusions:** Despite the limitation that the data is only from adults ≥ 45, this analysis provides important insights into the socioeconomic and housing variables associated with higher odds of dengue and CHIKV in India. Understanding these determinants may assist in the national planning of prevention and control strategies for dengue and CHIKV.

Clinical and laboratory characteristics of dengue and COVID-19 coinfected patients in Dhaka, Bangladesh.

Hannan, T., Hossain, Z., Hasan, M., Khan, A., Alam, M., Rahman, M., Arafat, S., Chowdhury, F.
20-04-2022
Trans R Soc Trop Med Hyg
https://pubmed.ncbi.nlm.nih.gov/35443278

Background: Dengue-COVID-19 coinfection is one of the greatest emerging challenges in dengue-endemic areas during the continuing pandemic. With coinciding clinical and laboratory pictures, early diagnosis becomes burdensome, with management discrepancy. Methods: A descriptive study was performed on dengue-COVID-19 coinfected patients during July-August 2021 for an overview of disease progression, severity and outcome. A total of 11 patients who were positive for dengue NS1 and/or antidengue IgM were included in this study. Results: In total, 45.5% patients developed severe COVID-19 disease, 45.5% patients developed group B dengue fever and 9% patients developed group C dengue fever. Concurrent severity of both diseases was seen to be rare, except for in one patient. Conclusion: Early diagnosis and compatible management still stand as basic principles to prevent fatality and morbidity.

Transplacental Zika virus transmission in ex vivo perfused human placentas.

Langerak, T., Broekhuizen, M., Unger, P., Tan, L., Koopmans, M., van Gorp, E., Danser, A., Rockx, B.
20-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010359

A Zika virus (ZIKV) infection during pregnancy can result in severe birth defects such as microcephaly. To date, it is incompletely understood how ZIKV can cross the human placenta. Furthermore, results from studies in pregnant mice and non-human primates are conflicting regarding the role of cross-reactive dengue virus (DENV) antibodies on transplacental ZIKV transmission. Elucidating how ZIKV can cross the placenta and which risk factors contribute to this is important for risk assessment and for potential intervention strategies for transplacental ZIKV transmission. In this study we use an ex vivo human placental perfusion model to study transplacental ZIKV transmission and the effect that cross-reactive DENV antibodies have on this transmission. By using this model, we demonstrate that DENV antibodies significantly increase ZIKV uptake in perfused human placentas and that this increased uptake is neonatal Fc-receptor-dependent. Furthermore, we show that cross-reactive DENV antibodies enhance ZIKV infection in term human placental explants and in primary fetal macrophages but not in primary trophoblasts. Our data supports the hypothesis that presence of cross-reactive DENV antibodies could be an important risk factor for transplacental ZIKV transmission. Furthermore, we demonstrate that the ex vivo placental perfusion model is a relevant and animal friendly model to study transplacental pathogen transmission.

Aedes aegypti abundance and insecticide resistance profiles in the applying Wolbachia to eliminate dengue trial.

Tantowijoyo, W., Tanamas, S., Nurhayati, I., Setyawan, S., Budiwati, N., Fitriana, I., Ernesia, I., Wardana, D., Supriyati, E., Arguni, E., Meitika, Y., Prabowo, E., Andari, B., Green, B., Hodgson, L., Rancès, E., Ryan, P., O'Neill, S., Anders, K., Ansari, M., Indriani, C., Ahmad, R., Utarini, A., Simmons, C.
20-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010284

The Applying Wolbachia to Eliminate Dengue (AWED) trial was a parallel cluster randomised trial that demonstrated Wolbachia (wMel) introgression into Ae. aegypti populations reduced dengue incidence. In this predefined substudy, we compared between treatment arms, the relative abundance of Ae. aegypti and Ae. albopictus before, during and after wMel-introgression. Between March 2015 and March 2020, 60,084 BG trap collections yielded 478,254 Ae. aegypti and 17,623 Ae. albopictus. Between treatment arms there was no measurable difference in Ae. aegypti relative abundance before or after wMel-deployments, with a count ratio of 0.96 (95% CI 0.76, 1.21) and 1.00 (95% CI 0.85, 1.17) respectively. More Ae. aegypti were caught per trap per week in the wMel-intervention arm compared to the control arm during wMel deployments (count ratio 1.23 (95% CI 1.03, 1.46)). Between treatment arms there was no measurable difference in the Ae. albopictus population size before, during or after wMel-deployment (overall count ratio 1.10 (95% CI 0.89, 1.35)). We also compared insecticide resistance phenotypes of Ae. aegypti in the first and second years after wMel-deployments. Ae. aegypti field populations from wMel-treated and untreated arms were similarly resistant to malathion (0.8%), permethrin (1.25%) and cyfluthrin (0.15%) in year 1 and year 2 of the trial. In summary, we found no between-arm differences in the relative abundance of Ae. aegypti or Ae. albopictus prior to or after wMel introgression, and no between-arm difference in Ae. aegypti insecticide resistance phenotypes. These data suggest neither Aedes abundance, nor insecticide resistance, confounded the epidemiological outcomes of the AWED trial.

Discovery and synthesis of 1,2,4-oxadiazole derivatives as novel inhibitors of Zika, dengue, Japanese encephalitis, and classical swine fever virus infections.

Nam, S., Na, H., Oh, E., Jung, E., Lee, Y., Jeong, E., Ou, Y., Zhou, B., Ahn, S., Shin, J., Han, S., Go, Y.
20-04-2022
Arch Pharm Res
https://doi.org/10.1007/s12272-022-01380-8

Zika virus (ZIKV), an arbovirus of the Flaviviridae family, has emerged as a significant public health concern owing to its

association with congenital abnormalities and severe neurological sequelae. Thus, there is an urgent need to develop effective therapeutic approaches to efficiently treat ZIKV infections. This study used phenotypic screening to identify a series of 1,2,4-oxadiazole derivatives that possess antiviral activity against ZIKV infection. Subsequently, 28 new derivatives were designed, synthesized, and evaluated for this purpose. Among these compounds, 4-(5-phenyl-1,2,4-oxadiazol-3-yl)-N-(pyridin-3-ylmethyl)aniline (5d) had potent antiviral activity against ZIKV infections. Furthermore, a structure-activity relationship analysis indicated that a benzyl substitution on the aniline nitrogen of this compound improved potency while augmenting its drug-like properties. In addition, 5d exhibited antiviral activity against various viruses of Flaviviridae family of worldwide public health importance, such as dengue, Japanese encephalitis and classical swine fever viruses, indicating its potential as a lead compound for generating 1,2,4-oxadiazole derivatives with broad-spectrum anti-flaviviral properties.

Urological outcomes in children with congenital Zika syndrome: the experience of a cohort in Campina Grande, Brazil.

Ferreira, R., Pinheiro, H., de Oliveira Melo, F., Gama, G., Monteiro, L., Fontes, J., de Oliveira Cruz, G., de Araújo, G., Amorim, M., Melo, A.
19-04-2022
Trop Med Int Health
https://doi.org/10.1111/tmi.13754

Objective: To describe the urological outcomes in children with congenital Zika syndrome (CZS) and investigate the relationship between clinical and urological findings in this population. Methods: This cross-sectional study involved children with CZS followed up by a referral center for children with microcephaly in the state of Paraiba in northeast Brazil. Urological evaluation included clinical history, urine culture results, ultrasonography of the urinary tract, and urodynamic evaluation, following the protocol proposed by Costa Monteiro et al. (2017). Descriptive statistical analysis was performed in addition to association and correlation tests, considering clinical and urodynamic variables. Results: Among the 88 children with CZS (35.5±5.5 months), 97.7% had microcephaly and 51% presented urinary tract infection (UTI) confirmed with clinical history and lab tests. The number of confirmed UTI episodes varied from one to 14 per child. Urodynamic evaluation confirmed the presence of an overactive bladder in 78 children and incomplete voiding in 50. Urodynamic findings were associated with the number of confirmed UTI episodes, child's sex, and actual weight, in addition to the use of anticonvulsant and myorelaxant drugs. Conclusions: UTIs were confirmed in most children. Other urological outcomes observed were overactive bladder and low bladder capacity, which were associated with the number of confirmed UTI episodes, use of anticonvulsants and myorelaxants, and the child's sex and weight. These are treatable conditions, and it is paramount that pediatricians, neonatologists, and infection disease specialists are aware of them to make clinical decisions and help reduce the risk of renal damage and other morbidities.

Ovipositional Reproduction of the Dengue Vector for Identifying High-Risk Urban Areas.

de Oliveira Lage, M., Barbosa, G., Andrade, V., Gomes, H., Chiaravalloti, F., Quintanilha, J.
19-04-2022
Ecohealth
https://doi.org/10.1007/s10393-022-01581-z

Identification and classification of high-risk areas for the presence of Aedes aegypti is not an easy task. To develop suitable methods to identify this areas is an essential task that will increase the efficiency and effectiveness of control measures and to optimize the use of resources. The objectives of this study were to identify high- risk areas for the presence of Ae. aegypti using mosquito traps and household visits to identify breeding sites; to identify and validate aspects of the remote sensing images that could characterize these areas; to evaluate the relationship between this spatial risk classification and the occurrence of Ae. aegypti; and provide a methodology to the health and control vector services and prioritize these areas for development of control measure. Information about the geographical coordinates of these traps will enable us to apply the kriging spatial analysis tool to generate maps with the predicted numbers of Ae. aegypti. Satellite images were used to identify the characteristic features the four areas, so that other areas could also be classified using only the sensing remote images. The developed methodology enables the identification of high-risk areas for Ae. aegypti and for the occurrence of Dengue, as well as Zika fever and Chikungunya fever using only sensing remote images. These results allow health and vector control services to prioritize these areas for developing surveillance and control measures. The use of the available resources can be optimized and potentially promote a decrease in the expected incidences of these diseases, particularly Dengue.

Measles-based Zika vaccine induces long-term immunity and requires NS1 antibodies to protect the female reproductive tract.

Kurup, D., Wirblich, C., Lambert, R., Diba, L., Leiby, B., Schnell, M.
19-04-2022
NPJ Vaccines
https://doi.org/10.1038/s41541-022-00464-2

Zika virus (ZIKV) can cause devastating effects in the unborn fetus of pregnant women. To develop a candidate vaccine that can protect human fetuses, we generated a panel of live measles vaccine (MV) vectors expressing ZIKV-E and -NS1. Our MV-based ZIKV-E vaccine, MV-E2, protected mice from the non-lethal Zika Asian strain (PRVABC59) and the lethal African strain (MR766) challenge. Despite 100% survival of the MV-E2 mice, however, complete viral clearance was not achieved in the brain and reproductive tract of the lethally challenged

mice. We then tested MV-based vaccines that expressed E and NS1 together or separately in two different vaccines. We observed complete clearance of ZIKV from the female reproductive tract and complete fetal protection in the lethal African challenge model in animals that received the dual antigen vaccines. Additionally, MV-E2 and MV-NS1, when administered together, induced durable plasma cell responses. Our findings suggest that NS1 antibodies are required to enhance the protection of ZIKV-E antibodies in the female reproductive tract.

Association between densities of adult and immature stages of Aedes aegypti mosquitoes in space and time: implications for vector surveillance.

Parra, M., Lorenz, C., Dibo, M., de Aguiar Milhim, B., Guirado, M., Nogueira, M., Chiaravalloti-Neto, F.
19-04-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05244-4

Background: Mosquito control is currently the main tool available to contain the spread of several arboviruses in Brazil. We have evaluated the association between entomological surveys of female adult Aedes aegypti and the Breteau index (BI) in space and time in a hyperendemic area, and compared the human resources costs required to measure each of these indicators. Methods: Entomological surveys were conducted between 2016 and 2019 in Vila Toninho, a neighborhood in the city of São José do Rio Preto, Brazil. Monthly records of collected mosquito specimens were made and then grouped by season. Results: Our findings showed that adult and immature mosquitoes are more related in time than in space, possibly due to differences in their habitats or in climate variables. Bayesian temporal modeling revealed that an increase in 1 standard deviation in the BI was associated with a 27% increase in the number of adult female mosquitoes when adjusted for climatic conditions. The cost of entomological surveys of adult mosquitoes was found to be 83% lower than the cost of determining the BI when covering the same geographic area. Conclusions: For fine-scale assessments, a simple measure of adult Ae. aegypti abundance may be more realistic than aquatic indicators, but the adult indices are not necessarily the only reliable measure. Surveying adult female mosquitoes has significant potential for optimizing vector control strategies because, unlike the BI, this tool provides an effective indicator for micro-areas within an urban region. It should be noted that the results of the present study may be due to specific features of of the study area, and future studies should analyze whether the patterns found in the study neighborhood are also found in other regions.

An E3 Ubiquitin Ligase Scaffolding Protein Is Proviral during Chikungunya Virus Infection in Aedes aegypti.

Dubey, S., Mehta, D., Chaudhary, S., Hasan, A., Sunil, S.
18-04-2022
Microbiol Spectr
https://doi.org/10.1128/spectrum.00595-22

Chikungunya virus (CHIKV) is a reemerging alphavirus causing chikungunya disease (CHIKD) and is transmitted to humans by *Aedes* mosquitoes. The virus establishes an intricate balance of cellular interactions that ultimately helps in its replication and dodges cellular immune response. In an attempt to identify cellular host factors required during CHIKV replication in Aag2 cells, we performed global transcriptomics of CHIKV-infected Aag2 cells, and further, we compared this library with the *Drosophila* RNAi Screening Center (DRSC) database and identified transcripts that were regulated in Aedes aegypti during CHIKV infection. These analyses revealed specific pathways, such as ubiquitin-related pathways, proteolysis pathways, protein catabolic processes, protein modification, and cellular protein metabolic processes, involved during replication of the virus. Loss-of-function assays of selected candidates revealed their proviral or antiviral characteristics upon CHIKV infection in A. aegypti-derived Aag2 cells. Further validations identified that the ubiquitin proteasomal pathway is required for CHIKV infection in A. aegypti and that an important member of this family of proteins, namely, AeCullin-3 (*Aedes* ortholog of human cullin-3), is a proviral host factor of CHIKV replication in Aag2 cells. IMPORTANCE Arboviruses cause several diseases in humans and livestock. Vector control is the main strategy for controlling diseases transmitted by mosquitoes. In this context, it becomes paramount to understand how the viruses replicate in the vector for designing better transmission blocking strategies. We obtained the global transcriptome signature of A. aegypti cells during CHIKV infection, and in order to obtain the maximum information from these data sets, we further utilized the well-characterized *Drosophila* system and arrived upon a set of transcripts and their pathways that affect A. aegypti cells during CHIKV infection. These analyses and further validations reveal that important pathways related to protein degradation are actively involved during CHIKV infection in A. aegypti and are mainly proviral. Targeting these molecules may provide novel approaches for blocking CHIKV replication in A. aegypti.

Isarubrolone C Promotes Autophagic Degradation of Virus Proteins via Activating ATG10S in HepG2 Cells.

Revue de littérature

Zhang, M., Li, L., Wu, L., Zhang, J.
24-02-2022
J Nat Prod
https://doi.org/10.1021/acs.jnatprod.1c01161

Isarubrolone C is a bioactive polycyclic tropoloalkaloid from *Streptomyces*. Our previous study showed that isarubrolone C could trigger autophagy. Here, we report isarubrolone C potential in broad-spectrum antiviral effect and its antiviral mechanism *in vitro*. Our results show that isarubrolone C activated autophagy and reduced levels of viral proteins in the cells harboring HCV-CORE/NS5B, HBx, ZIKV-NS5, and HIV-RT,

respectively. The role of isarubrolone C in suppression of the viral proteins was via an autophagic degradation pathway rather than a proteasome pathway. Co-immunoprecipitation assays revealed that isarubrolone C promoted both autophagy flux opening and the viral proteins being enwrapped in autolysosomes. PCR assays showed that isarubrolone C elevated the transcription levels of *ATG10/ATG10S* and *IL28A*. Further, ATG10S high expression could efficiently enhance IL28A expression and the ability of isarubrolone C to degrade the viral proteins by promoting the colocalization of viral proteins with autolysosomes. Additionally, knockdown of endogenous *IL28A* caused both losses of the isarubrolone C antiviral effect and autolysosome formation. These results indicate that the role of isarubrolone C antiviruses is achieved by triggering the autophagic mechanism, which is mediated by endogenous ATG10S and IL28A activation. This is the first report about isarubrolone C potential of *in vitro* broad-spectrum antiviruses.

'Double doughnut' sign in Japanese encephalitis.

Suresh, S., Pannu, A., Arora, N., Chabra, M.
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QJM
https://doi.org/10.1093/qjmed/hcac054

Biochemical Screening of Potent Zika Virus Protease Inhibitors.

Coelho, C., Gallo, G., Hardy, L., Bottazzi, M., Campos, C., Würtele, M.
09-02-2022
ChemMedChem
https://doi.org/10.1002/cmdc.202100695

As the Zika virus protease is an essential and well-established target for the development of antiviral agents, we biochemically screened for inhibitors using a purified recombinantly expressed form of this enzyme. As a result, we were able to identify 10 new Zika virus protease inhibitors. These compounds are natural products and showed strong inhibition in the biochemical assays. Inhibitory constants values for the compounds ranged from 5 nM to 8 μM. Among the most potent inhibitors are flavonoids like irigenol hexa-acetate (K_i =0.28 μM), katacine (K_i =0.26 μM), theaflavin gallate (K_i =0.40 μM) and hematein (K_i =0.33 μM). Inhibitors from other groups of natural products include sennoside A (K_i =0.19 μM) and gossypol (K_i =0.70 μM). Several of the obtained compounds are known for their beneficial health effects and have acceptable pharmacokinetic characteristics. Thus, they could be of interest as lead compounds for the development of important and essential Zika antiviral drugs.

RAGE

Louis Pasteur: Between Myth and Reality.

Revue de littérature

Cavaillon, J., Legout, S.
18-04-2022
Biomolecules
https://pubmed.ncbi.nlm.nih.gov/35454184

Louis Pasteur is the most internationally known French scientist. He discovered molecular chirality, and he contributed to the understanding of the process of fermentation, helping brewers and winemakers to improve their beverages. He proposed a process, known as pasteurization, for the sterilization of wines. He established the germ theory of infectious diseases that allowed Joseph Lister to develop his antiseptic practice in surgery. He solved the problem of silkworm disease, although he had refuted the idea of Antoine Béchamp, who first considered it was a microbial infection. He created four vaccines (fowl cholera, anthrax, pig erysipelas, and rabies) in the paths of his precursors, Henri Toussaint (anthrax vaccine) and Pierre Victor Galtier (rabies vaccine). He generalized the word "vaccination" coined by Richard Dunning, Edward Jenner's friend. Robert Koch, his most famous opponent, pointed out the great ambiguity of Pasteur's approach to preparing his vaccines. Analysis of his laboratory notebooks has allowed historians to discern the differences between the legend built by his hagiographers and reality. In this review, we revisit his career, his undeniable achievements, and tell the truth about a hero who made every effort to build his own fame.

Inhibitory effect of concomitantly administered rabies immunoglobulins on the immunogenicity of commercial and candidate human rabies vaccines in hamsters.

Bernard, M., Boudet, F., Pineda-Peña, A., Guinet-Morlot, F.
21-04-2022
Sci Rep
https://doi.org/10.1038/s41598-022-10281-1

The World Health Organization protocol for rabies post-exposure prophylaxis (PEP) recommends extensive wound washing, immediate vaccination, and administration of rabies immunoglobulin (RIG) in severe category III exposures. Some studies have shown that RIG can interfere with rabies vaccine immunogenicity to some extent. We investigated the interference of RIG on a next generation highly purified Vero cell rabies vaccine candidate (PVRV-NG) versus standard-of-care vaccines in a previously described hamster model. The interference of either human (h) or equine (e) RIG on the immune response elicited by PVRV-NG, Verorab® (purified Vero cell rabies vaccine, PVRV), and Imovax® Rabies (human diploid cell rabies vaccine; HDCV) was evaluated using the 4-dose Essen PEP regimen. The anti-rabies seroneutralizing titers and specific serum IgM titers were measured by fluorescent antibody virus neutralization test and enzyme-

linked immunosorbent assay, respectively, for the vaccines administered with or without RIG. The RIG interference on PVRV-NG, observed transiently at Day 7, was similar to that on PVRV and tended to be lower than that on HDCV using both read-outs. In summary, the results generated in the hamster model showed that RIG induced similar or less interference on PVRV-NG than the standard-of-care vaccines.

One step closer to a transmissible vaccine for rabies virus.

Nuismer, S.
20-04-2022
PLoS Biol
https://doi.org/10.1371/journal.pbio.3001607

A recent study in PLOS Biology shows that a betaherpesvirus circulating with the vampire bat, Desmodus rotundus, could serve as an effective vector for a transmissible vaccine capable of reducing the risk of rabies virus spillover in Peru.

Longitudinal deep sequencing informs vector selection and future deployment strategies for transmissible vaccines.

Griffiths, M., Broos, A., Bergner, L., Meza, D., Suarez, N., da Silva Filipe, A., Tello, C., Becker, D., Streicker, D.
19-04-2022
PLoS Biol
https://doi.org/10.1371/journal.pbio.3001580

Vaccination is a powerful tool in combating infectious diseases of humans and companion animals. In most wildlife, including reservoirs of emerging human diseases, achieving sufficient vaccine coverage to mitigate disease burdens remains logistically unattainable. Virally vectored "transmissible" vaccines that deliberately spread among hosts are a potentially transformative, but still theoretical, solution to the challenge of immunising inaccessible wildlife. Progress towards real-world application is frustrated by the absence of frameworks to guide vector selection and vaccine deployment prior to major in vitro and in vivo investments in vaccine engineering and testing. Here, we performed deep sequencing on field-collected samples of Desmodus rotundus betaherpesvirus (DrBHV), a candidate vector for a transmissible vaccine targeting vampire bat-transmitted rabies. We discovered 11 strains of DrBHV that varied in prevalence and geographic distribution across Peru. The phylogeographic structure of DrBHV strains was predictable from both host genetics and landscape topology, informing long-term DrBHV-vectored vaccine deployment strategies and identifying geographic areas for field trials where vaccine spread would be naturally contained. Multistrain infections were observed in 79% of infected bats. Resampling of marked individuals over 4 years showed within-host persistence kinetics characteristic of latency and reactivation, properties that might boost individual immunity and lead to sporadic vaccine transmission over the lifetime of the host. Further, strain acquisitions by already infected individuals implied that preexisting immunity and strain competition are unlikely to inhibit vaccine spread. Our results support the development of a transmissible vaccine targeting a major source of human and animal rabies in Latin America and show how genomics can enlighten vector selection and deployment strategies for transmissible vaccines.

Commentary on the implications of safety and efficacy studies in pediatric patients with administration of human rabies immune globulin (HRIG)?

Siegel, J., Kappeler, K.
19-04-2022
Hum Vaccin Immunother
https://doi.org/10.1080/21645515.2022.2054262

The FDA strongly encourages rigorous safety and efficacy studies in all age groups for which vaccines and treatments for pervasive and severe diseases are intended. Until recently, there had been no safety and efficacy studies conducted in children for human rabies immune globulins. The publication," Safety, and efficacy of rabies immunoglobulin in pediatric patients with suspected exposure", Human Vaccines & Immunotherapeutics, 17:7, 2090-2096, was the first study that prospectively reviewed the use of KEDRAB® 150 IU/ml in 30 pediatric patients ages 0.5-14.9years old. The results showed that 93.3% achieved RVNA titer >/=5 IU/ml, on day 14. Also, no participants reported a serious adverse event (SAE), or an adverse event (AE) leading to study discontinuation, and there were no deaths. The most common treatment emergent adverse events (TEAE) were injection-site pain. Currently there are 3 HRIG products on the US market, KEDRAB®, HyperRab® and Imogam® Rabies HT, but only KEDRAB® has published safety and efficacy data in a pediatric population. While it is common practice to prescribe medications for pediatric patients "off-label" there now exists one product with safety data in children. It is worth considering if this creates a higher medical liability for the prescriber and institution.

Novel Duplex RT-qPCR for animal rabies surveillance.

Minozzo, G., Corona, T., da Cruz, E., de Castro, W., Kmetiuk, L., Pires Dos Santos, A., Biondo, A., Riediger, I.
19-04-2022
Transbound Emerg Dis
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Rabies is a lethal zoonosis affecting mammals worldwide. Diagnosis of rabies follows international standard protocols, primarily relying on direct immunofluorescence (DI) followed by mouse inoculation test (MIT). WHO recommends molecular biology techniques such as RT-qPCR for replacing MIT to diagnose rabies in animal samples. Recently, a real-time PCR protocol that detects all rabies virus variants identified worldwide was validated. This assay is a Pan-Lyssavirus Taqman quantitative RT-PCR called LN34. A modified LN34

assay protocol was tested at the Paraná State Reference Laboratory (Lacen/PR) using animal samples previously tested by DI and MIT, the Gold Standard (GS). This method has been changed to a RT-qPCR duplex format to better fit the diagnostic routine. The new assay was called Duplex LN34 and β-actin RT-qPCR. All the 88 samples evaluated using the GS test, modified pan-Lyssavirus TaqMan RT-qPCR, and Duplex LN34 and β-actin RT-qPCR showed 100% agreement with each other. This novel duplex RT-qPCR protocol has shown adequate diagnostic performance and may be used in research and surveillance purposes, replacing the standard MIT, and ending mice use for rabies diagnosis. This article is protected by copyright. All rights reserved.

Dendritic Domain-Specific Sampling of Long-Range Axons Shapes Feedforward and Feedback Connectivity of L5 Neurons.

Galloni, A., Ye, Z., Rancz, E.
03-03-2022
J Neurosci
https://doi.org/10.1523/JNEUROSCI.1620-21.2022

Feedforward and feedback pathways interact in specific dendritic domains to enable cognitive functions such as predictive processing and learning. Based on axonal projections, hierarchically lower areas are thought to form synapses primarily on dendrites in middle cortical layers, whereas higher-order areas are thought to target dendrites in layer 1 and in deep layers. However, the extent to which functional synapses form in regions of axodendritic overlap has not been extensively studied. Here, we use viral tracing in the secondary visual cortex of male mice to map brain-wide inputs to thick-tufted layer 5 pyramidal neurons. Furthermore, we provide a comprehensive map of input locations through subcellular optogenetic circuit mapping. We show that input pathways target distinct dendritic domains with far greater specificity than appears from their axonal branching, often deviating substantially from the canonical patterns. Common assumptions regarding the dendrite-level interaction of feedforward and feedback inputs may thus need revisiting.SIGNIFICANCE STATEMENT Perception and learning depend on the ability of the brain to shape neuronal representations across all processing stages. Long-range connections across different hierarchical levels enable diverse sources of contextual information, such as predictions or motivational state, to modify feedforward signals. Assumptions regarding the organization of this hierarchical connectivity have not been extensively verified. Here, we assess the synaptic connectivity of brain-wide projections onto pyramidal neurons in the visual cortex of mice. Using trans-synaptic viral tracing and subcellular optogenetic circuit mapping, we show that functional synapses do not follow the consistent connectivity rule predicted by their axonal branching patterns. These findings highlight the diversity of computational strategies operating throughout cortical networks and may aid in building better artificial networks.

TRACHOME

A national survey integrating clinical, laboratory, and WASH data to determine the typology of trachoma in Nauru.

Lynch, K., Apadinuwe, S., Lambert, S., Hillgrove, T., Starr, M., Catlett, B., Ware, R., Cama, A., Webster, S., Harding-Esch, E., Bakhtiari, A., Butcher, R., Cunningham, P., Martin, D., Gwyn, S., Solomon, A., Garabwan, C., Kaldor, J., Vaz Nery, S.
19-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010275

Background: The epidemiology of trachoma in several Pacific Islands differs from other endemic settings, in that there is a high prevalence of clinical signs of trachoma, particularly trachomatous inflammation-follicular (TF), but few cases of trichiasis and limited evidence of ocular chlamydial infection. This so-called "Pacific enigma" has led to uncertainty regarding the appropriate public health response. In 2019 alongside Nauru's national trachoma population survey, we performed bacteriological and serological assessments of children to better understand the typology of trachoma and to determine whether there is a need for trachoma interventions. Methods: We used two-stage cluster sampling, examining residents aged ≥1 year and collecting household-level water, sanitation, and hygiene (WASH) variables. Children aged 1-9 years provided conjunctival swabs and finger-prick dried blood spots to investigate the presence of Chlamydia trachomatis nucleic acid and anti-Pgp3 antibodies, respectively. Principal findings: In 818 participants aged 1-9 years, the age-adjusted TF prevalence was 21.8% (95% CI 15.2-26.2%); ocular C. trachomatis prevalence was 34.5% (95% CI 30.6-38.9), and anti-Pgp3 antibody prevalence was 32.1% (95% CI 28.4%-36.3%). The age- and gender-adjusted prevalence of trichiasis in ≥15-year-olds was 0.3% (95% CI 0.00-0.85), but no individual with trichiasis had trachomatous scarring (TS). Multivariable analysis showed an association between age and both TF (OR per year of age 1.3 [95% CI 1.2-1.4]) and anti-Pgp3 positivity (OR 1.2 [95% CI 1.2-1.3]). There were high rates of access to water and sanitation and no WASH variable was associated with the presence of TF. Conclusions: TF, nucleic acid, and age-specific antibody prevalence collectively indicate that high levels of C. trachomatis transmission among children present a high risk of ocular damage due to trachoma. The absence of trichiasis with trachomatous scarring suggest a relatively recent increase in transmission intensity.

ULCERE DE BURULI

Possum bites man: case of Buruli ulcer following possum bite.

Xu, R., Stinear, T., Johnson, P., O'Brien, D.

20-04-2022
Med J Aust
https://doi.org/10.5694/mja2.51505

Molecular Characterization of Mycobacterium ulcerans DNA Gyrase and Identification of Mutations Reducing Susceptibility to Quinolones *In Vitro*.

Kim, H., Mori, S., Kenri, T., Suzuki, Y.
18-01-2022
Antimicrob Agents Chemother
https://doi.org/10.1128/AAC.01902-21

Buruli ulcer disease is a neglected necrotizing and disabling cutaneous tropical illness caused by Mycobacterium ulcerans. Fluoroquinolone (FQ), used in the treatment of this disease, has been known to act by inhibiting the enzymatic activities of DNA gyrase. However, the detailed molecular basis of these characteristics and the FQ resistance mechanisms in M. ulcerans remains unknown. This study investigated the detailed molecular mechanism of M. ulcerans DNA gyrase and the contribution of FQ resistance *in vitro* using recombinant proteins from the M. ulcerans subsp. shinshuense and Agy99 strains with reduced sensitivity to FQs. The IC_{50} of FQs against Ala91Val and Asp95Gly mutants of M. ulcerans shinshuense and Agy99 GyrA subunits were 3.7- to 42.0-fold higher than those against wild-type (WT) enzyme. Similarly, the quinolone concentrations required to induce 25% of the maximum DNA cleavage (CC_{25}) was 10- to 210-fold higher than those for the WT enzyme. Furthermore, the interaction between the amino acid residues of the WT/mutant M. ulcerans DNA gyrase and FQ side chains were assessed by molecular docking studies. This was the first elaborative study demonstrating the contribution of mutations in M. ulcerans DNA GyrA subunit to FQ resistance *in vitro*.

PIAN

LEPRE

Territory, neglected diseases and the action of community and endemic combat agents.

García, G., Souza, E., Araújo, V., Macedo, M., Andrade, R., Ferreira, P., Guimarães, M., Silva, J., Ramos Júnior, A.
22-04-2022
Rev Saude Publica
https://pubmed.ncbi.nlm.nih.gov/35476105

Objective: To characterize knowledge, practices, and professional experience of community health agents (ACS) and endemic combat agents (ACE) on leprosy and Chagas disease (DC), during participation in an integrated training workshop in the IntegraDTNs-Bahia project. Methods: Descriptive and exploratory case study, involving health agents and endemic combat agents participating in a training workshop on the shared role of these professionals in health care and surveillance processes. The project was developed in the municipalities of Anagé, Tremedal and Vitória da Conquista, in the southwestern State of Bahia, 2019-2020. A specific instrument was applied, with questions related to knowledge and practices of surveillance and care for leprosy and Chagas disease. Descriptive analysis of the data, in addition to consolidation of the lexical analysis, was performed. Results: Out of a total of 135 participants (107 ACS and 28 ACE), 80.7% of them have been working for at least 12 years, without previous participation in joint training processes. Only 17.9% of endemic combat agentes reported having participated in training on leprosy and none reported developing specific actions to control the disease. For Chagas disease, 36.4% of community health agents participated in training more than a decade before, while for 60.7% of endemic combat agents the last training was carried out in the last five years. The development of educational actions for Chagas disease was more frequent for endemic combat agents (64.3%). When asked about ways of recognizing diseases, the term "skin spots" was the most reported (38 times) for leprosy and, for Chagas disease, the term "I don't know" (17 times). Conclusion: Processes of health agents and endemic combat agents action in realities endemic for leprosy and Chagas disease in the interior of Bahia proved to be fragmented in the territories. For these diseases, the distance between surveillance and health care actions is reinforced, including in training processes. The importance of innovative permanent and integrated education actions is reiterated to actually promote changes in practices.

Temporal evolution and spatial distribution of leprosy in a municipality with low endemicity in São Paulo state, Brazil.

Ramos, A., Martoreli Júnior, J., Berra, T., Alves, Y., Barbosa, T., Scholze, A., Assis, I., Palha, P., Gomes, D., Arcêncio, R.
20-04-2022
Epidemiol Serv Saude
https://pubmed.ncbi.nlm.nih.gov/35476004

To analyze the spatial and temporal distribution of leprosy in a scenario of low endemicity in the state of São Paulo, Brazil. Ecological study with leprosy cases in Ribeirão Preto, between 2006 to 2016. The temporal trend of leprosy detection was verified through the decomposition of time series and identified areas of high and low occurrence of the disease using the Getis-Ord Gi* technique. There were 890 cases, and the detection rate showed an increasing trend in the period from 2011 to 2015, with an average growth of 1% per month. Areas of high occurrence of the disease were identified in the northern region of the city (99% and 95% confidence). The temporal analysis showed that the rate of detection of leprosy presented an increasing trend, and the spatial analysis showed that the region of the municipality with the highest

occurrence of the disease is characterized by presenting the greatest social inequalities.

Circulation, sensation, and hair growth-A reply.

Cavanagh, G., Goren, A., Wambier, C.
23-04-2022
J Am Acad Dermatol
https://pubmed.ncbi.nlm.nih.gov/35472324

Construction and Analysis of the Complete Genome Sequence of Leprosy Agent Mycobacterium lepromatosis.

Silva, F., Santos-Garcia, D., Zheng, X., Zhang, L., Han, X.
25-04-2022
Microbiol Spectr
https://doi.org/10.1128/spectrum.01692-21

Leprosy is caused by Mycobacterium leprae and Mycobacterium *lepromatosis*. We report construction and analyses of the complete genome sequence of *M. lepromatosis* FJ924. The genome contained 3,271,694 nucleotides to encode 1,789 functional genes and 1,564 pseudogenes. It shared 1,420 genes and 885 pseudogenes (71.4%) with M. leprae but differed in 1,281 genes and pseudogenes (28.6%). In phylogeny, the leprosy bacilli started from a most recent common ancestor (MRCA) that diverged ~30 million years ago (Mya) from environmental organism Mycobacterium haemophilum. The MRCA then underwent reductive evolution with pseudogenization, gene loss, and chromosomal rearrangements. Analysis of the shared pseudogenes estimated the pseudogenization event ~14 Mya, shortly before species bifurcation. Afterwards, genomic changes occurred to lesser extent in each species. Like M. leprae, four major types of highly repetitive sequences were detected in *M. lepromatosis*, contributing to chromosomal rearrangements within and after MRCA. Variations in genes and copy numbers were noted, such as three copies of the gene encoding bifunctional diguanylate cyclase/phosphodiesterase in *M. lepromatosis*, but single copy in M. leprae; 6 genes encoding the TetR family transcriptional regulators in *M. lepromatosis*, but 11 such genes in M. leprae; presence of *hemW* gene in *M. lepromatosis*, but absence in M. leprae; and others. These variations likely aid unique pathogenesis, such as diffuse lepromatous leprosy associated with *M. lepromatosis*, while the shared genomic features should explain the common pathogenesis of dermatitis and neuritis in leprosy. Together, these findings and the genomic data of *M. lepromatosis* may facilitate future research and care for leprosy. IMPORTANCE Leprosy is a dreaded infection that still affects millions of people worldwide. Mycobacterium *lepromatosis* is a recently recognized cause in addition to the well-known Mycobacterium leprae. *M. lepromatosis* is likely specific for diffuse lepromatous leprosy, a severe form of the infection and endemic in Mexico. This study constructed and annotated the complete genome sequence of *M. lepromatosis* FJ924 and performed comparative genomic analyses with related mycobacteria. The results afford new and refined insights into the genome size, gene repertoire, pseudogenes, phylogenomic relationship, genome organization and plasticity, process and timing of reductive evolution, and genetic and proteomic basis for pathogenesis. The availability of the complete *M. lepromatosis* genome may prove to be useful for future research and care for the infection.

Analysis of therapeutic effectiveness and adverse effects of long-term corticosteroids among leprosy patients with reactions: A retrospective cohort study.

Siagian, J., Purwantyastuti, ., Instiaty, ., Menaldi, S.
19-04-2022
SAGE Open Med
https://doi.org/10.1177/20503121221089448

Objectives: Main therapy for leprosy reactions is 12 weeks corticosteroids according to World Health Organization recommendations, but recovery cannot be achieved and recurrence occurs. Long duration of administration was thought to provide better clinical improvement. Evidence of the efficacy of corticosteroids in leprosy reactions is still lacking, and optimal dose and duration of therapy vary, while the need for long-term high-dose corticosteroids makes it difficult to avoid adverse effects. Methods: This is a retrospective cohort study analyzing the difference between therapeutic effectiveness and adverse effects of 12 weeks and >12 weeks corticosteroids, involving all new leprosy patients without age restriction, at Cipto Mangunkusumo Hospital and Cakung Community Health Center in Indonesia during 1 January 2015-31 December 2017. Secondary data were collected from medical records, and observations carried out until December 2018. Therapeutic effectiveness was assessed from clinical improvement to corticosteroids discontinuation, without 3 months recurrence after first cycle was completed. Adverse effects were assessed by all corticosteroids-related side effects. Results: Of 195 patients, 57 (29.2%) used 12 weeks corticosteroids, and 138 (70.8%) for >12 weeks. Effectiveness occurred in 38 (66.7%) of 12 weeks group and 106 (76.8%) of >12 weeks group (relative risk=0.604, 95% confidence interval=0.307-1.189, p=0.143). Of 145 patients, adverse effects occurred in 12 (31.6%) of 12 weeks group and 70 (65.4%) of >12 weeks group (relative risk=0.244, 95% confidence interval=0.111-0.538, p<0.001). Of 171 adverse effects, 37.4% were mild such as dyspepsia, skin disorders, and lipodystrophy, while 62.6% were severe in the form of neuropsychiatric disorders, eye disorders, cardiovascular disease, gastrointestinal bleeding, metabolic-hormonal abnormalities, and reactivation of infections. Conclusion: There is no effectiveness difference in the form of clinical improvement without 3 months recurrence, between 12 weeks and >12 weeks corticosteroid, while longer administration causes 4 times more events.

Reduced vitamin D receptor (VDR) and cathelicidin antimicrobial peptide (CAMP) gene expression contribute to the maintenance of inflammatory immune response in leprosy patients.

Grossi de Oliveira, A., Chaves, A., Cardoso, M., Gomide Pinheiro, G., Antunes, D., Aparecida de Faria Grossi, M., Lyon, S., Bueno, L., Otávio da Costa Rocha, M., Alves da Silva Menezes, C., Fujiwara, R.
21-04-2022
Microbes Infect
https://pubmed.ncbi.nlm.nih.gov/35462022

Leprosy is an infectious disease influenced by genetic, immunological, and environmental factors. Reduced gene expressions may be associated with the immunological response pattern and leprosy susceptibility. We investigated the direct and indirect effects of Vitamin D Receptor (VDR) and Cathelicidin Antimicrobial Peptide (CAMP) gene expressions on the serum levels of vitamin D, Cathelicidin, and cytokines in newly-diagnosed leprosy patients and post-six-months of multidrug therapy (MDT). Thirty-four leprosy patients were assessed, paucibacillary (PB; n=14) and multibacillary (MB; n=20) cases, untreated or having received six months of MDT, 18 healthy controls, and 25 household contacts. VDR and CAMP gene expression levels were strongly correlated to some important cytokines in both, untreated leprosy patients (PB, r = 0.9319; MB, r =0.9569) and patients who had undergone MDT (PB, r = 0.9667; MB, r = 0.9569). We observed that both gene expressions directly influenced IL-2, IFN-γ, and IL-17F serum levels in leprosy patients compared to the household contacts and healthy individuals. VDR and CAMP gene expressions induced a persistent inflammatory response in PB and MB leprosy patients, even after six months of MDT, to fight the Mycobacterium leprae infection. Due to the persistent inflammatory profile, multidrug therapy is suggested to be maintained for more than six months, especially for MB patients. Vitamin D supplementation is recommended from the onset as a transcription factor to improve VDR and CAMP gene expression in leprosy patients.

Picturing health: the burden of leprosy in eastern Indonesia.

Pieter, Y., Grijsen, M.
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Lancet
https://pubmed.ncbi.nlm.nih.gov/35461546

In the footsteps of Albert Calmette: an ecological study of TB, leprosy and potential exposure to wild-type Mycobacterium bovis.

Pépin, J., Fox, A., LeBlanc, L., De Wals, P., Rousseau, M.
23-04-2022
Trans R Soc Trop Med Hyg
https://pubmed.ncbi.nlm.nih.gov/35460554

Background: One hundred years ago, Albert Calmette developed an avirulent strain of Mycobacterium bovis, but there is no evidence that his BCG strain was more immunogenic than wild-type M. bovis. Geographic variations in BCG efficacy remain ill-understood. We hypothesized that exposure to M. bovis through unpasteurized milk might protect against Mycobacterium tuberculosis and Mycobacterium leprae. Methods: After excluding high-income countries (with universal milk pasteurization) and microstates, an ecological study comprising 113 countries was conducted. National data were obtained from United Nations agencies and international organizations about milk production per capita (1980-1999) as a proxy for exposure to wild-type M. bovis, TB (2000-2019) and leprosy (2005-2019) incidence, HIV prevalence (2000-2019), human development index (2010), global hunger index (2010), neonatal BCG coverage (1980-1999), urbanization (2000) and temperature (1990-2020). Multiple linear regression analyses were performed using log-transformed variables. Results: For TB, the association differed by region. An inverse association with milk production was seen in regions outside, but not within, sub-Saharan Africa, after adjustment for confounders. The incidence of leprosy was inversely associated with milk production when combining all countries, but the association was stronger in sub-Saharan Africa. Conclusions: Exposure to wild-type M. bovis through unpasteurized milk may provide cross-protection against M. tuberculosis and M. leprae and contribute to geographic disparities in BCG efficacy. This needs to be confirmed by individual-level studies.

Comprehensive polyoxypregnane glycosides report in Caralluma quadrangula using UPLC-ESI-Q-TOF and their antioxidant effects in human plasma.

Hamed, A., Ben Said, R., Ben Aissa, M., Abdel-Farid, I., Kontek, B., Kowalczyk, M., Oleszek, W., Stochmal, A., Kowalska, I., Olas, B.
18-04-2022
Biomed Pharmacother
https://pubmed.ncbi.nlm.nih.gov/35447547

Ethnopharmacological relevance: Caralluma quadrangula (Forssk.) N.E.Br. (Syns: = Stapelia quadrangula Forssk. = Monolluma quadrangula Forssk.) is an indigenous member of the genus Caralluma and it is a rather common species on rocky hillsides in the southwestern part of Saudi Arabia. Several members of this genus have found medicinal uses in the treatment of rheumatism, diabetes, leprosy and as antiseptics and disinfectants. All parts are edible but rather more bitter and can cause diarrhea. Aim of the study: The present report was tentatively elucidated the structure of acylated and non-acylated polyoxypregnane glycosides from Caralluma quadrangula. Materials and methods: The analyses were performed using an electrospray-ionization quadrupole time-of-flight (ESI-Q-TOF) mass spectrometer in both positive and negative ionization modes to explore fragmentation pathways. The antioxidant and prooxidant properties of the different mobility portions of human plasma were evaluated in vitro using thiobarbituric acid reactive substance assay (TBARS). Results: The analyses showed sixty-five characteristic ion peaks which could be more efficient to assignment the

aglycones and fragmentation sequences of sugar moieties. The used ionization modes provided consistent and/or complementary information for most of the pregnane glycosides, their fragmentation sequences, and their aglycones. A DFT Study was performed to elucidate the neutral loss of H_2O molecules sequences from aglycones and the esterification linkage. Conclusions: This report could be useful to reduce material consuming and time in phytochemistry analysis of the different medicinal plants. The two portions significantly depleted TBARS were subjected to autoperoxidation assay in the presence of hydrogen peroxide.

Development of anxiolytic and depression-like behavior in mice infected with mycobacterium lepraemurium.

Ponce-Regalado, ., Salazar-Juárez, A., Oscar, R., Contis-Montes de Oca, A., Hurtado-Alvarado, G., Arce-Paredes, P., Pérez-Sánchez, G., Pavón, L., Girón-Pérez, M., Hernández-Pando, R., Alvarez-Sánchez, M., Enrique, B.
18-04-2022
Neuroscience
https://pubmed.ncbi.nlm.nih.gov/35447197

Murine leprosy is a systemic infectious disease of mice caused by Mycobacterium lepraemurium (MLM) in which the central nervous system (CNS) is not infected; nevertheless, diseased animals show measurable cognitive alterations. For this reason, in this study, we explored the neurobehavioral changes in mice chronically infected with MLM. BALB/c mice were infected with MLM, and 120 days later, the alterations in mice were evaluated based on immunologic, histologic, endocrine, neurochemical, and behavioral traits. We found increases in the levels of IL-4 and IL-10 associated with high bacillary loads. We also found increase in the serum levels of corticosterone, epinephrine, and norepinephrine in the adrenal gland, suggesting neuroendocrine deregulation. Mice exhibited depression-like behavior in the tail suspension and forced swimming tests and anxiolytic behavior in the open field and elevated plus maze tests. The neurobehavioral alterations of mice were correlated with the histologic damage in the prefrontal cortex, ventral hippocampus, and amygdala, as well as with a blood-brain barrier disruption in the hippocampus. These results reveal an interrelated response of the neuroimmune-endocrinological axis in unresolved chronic infections that result in neurocognitive deterioration.

TRYPANOSOMES (TRYPANOSOMIASE ET MALADIE DE CHAGAS)

Territory, neglected diseases and the action of community and endemic combat agents.

García, G., Souza, E., Araújo, V., Macedo, M., Andrade, R., Ferreira, P., Guimarães, M., Silva, J., Ramos Júnior, A.
22-04-2022
Rev Saude Publica
https://pubmed.ncbi.nlm.nih.gov/35476105

Objective: To characterize knowledge, practices, and professional experience of community health agents (ACS) and endemic combat agents (ACE) on leprosy and Chagas disease (DC), during participation in an integrated training workshop in the IntegraDTNs-Bahia project. Methods: Descriptive and exploratory case study, involving health agents and endemic combat agents participating in a training workshop on the shared role of these professionals in health care and surveillance processes. The project was developed in the municipalities of Anagé, Tremedal and Vitória da Conquista, in the southwestern State of Bahia, 2019-2020. A specific instrument was applied, with questions related to knowledge and practices of surveillance and care for leprosy and Chagas disease. Descriptive analysis of the data, in addition to consolidation of the lexical analysis, was performed. Results: Out of a total of 135 participants (107 ACS and 28 ACE), 80.7% of them have been working for at least 12 years, without previous participation in joint training processes. Only 17.9% of endemic combat agentes reported having participated in training on leprosy and none reported developing specific actions to control the disease. For Chagas disease, 36.4% of community health agents participated in training more than a decade before, while for 60.7% of endemic combat agents the last training was carried out in the last five years. The development of educational actions for Chagas disease was more frequent for endemic combat agents (64.3%). When asked about ways of recognizing diseases, the term "skin spots" was the most reported (38 times) for leprosy and, for Chagas disease, the term "I don't know" (17 times). Conclusion: Processes of health agents and endemic combat agents action in realities endemic for leprosy and Chagas disease in the interior of Bahia proved to be fragmented in the territories. For these diseases, the distance between surveillance and health care actions is reinforced, including in training processes. The importance of innovative permanent and integrated education actions is reiterated to actually promote changes in practices.

Trypanosoma cruzi strain and starvation-driven mitochondrial RNA editing and transcriptome variability.

Gerasimov, E., Ramirez-Barrios, R., Yurchenko, V., Zimmer, S.
25-04-2022
RNA
https://pubmed.ncbi.nlm.nih.gov/35470233

Trypanosoma cruzi is a unicellular protistan parasitic species that is comprised of strains and isolates exhibiting high levels of genetic and metabolic variability. In the insect vector, it is known to be highly responsive to starvation, a signal for progression to a life stage in which it can infect mammalian cells. Most mRNAs encoded in its mitochondrion require the targeted insertion and deletion of uridines to become

translatable transcripts. This study defined differences in uridine-insertion/deletion RNA editing among three strains and established the mechanism whereby abundances of edited (and, thus, translatable) mitochondrial gene products increase during starvation. Our approach utilized our custom T-Aligner toolkit to describe transcriptome-wide editing events and reconstruct editing products from high-throughput sequencing data. We found that the relative abundance of mitochondrial transcripts and the proportion of mRNAs that are edited varies greatly between analyzed strains, a characteristic that could potentially impact metabolic capacity. Starvation typically led to an increase in overall editing activity rather than affecting a specific step in the process. We also determined that transcripts *CR3*, *CR4*, and *ND3* produce multiple open reading frames that, if translated, would generate different proteins. Finally, we quantitated the inherent flexibility of editing in *T. cruzi* and found it to be higher relative to that in a related trypanosomatid lineage. Over time, new editing domains or patterns could prove advantageous to the organism and become more widespread within individual transcriptomes or among strains.

Chloride substitution on 2-hydroxy-3,4,6-trimethoxyphenylchalcones improves in vitro selectivity on Trypanosoma cruzi strain Y.

Magalhães, E., Barroso Gomes, N., Araújo de Freitas, T., Silva, B., Ribeiro, L., Queiroz Ameida-Neto, F., Marinho, M., de Lima-Neto, P., Marinho, E., Silva Dos Santos, H., Rodrigues Teixeira, A., Sampaio, T., Paula Pessoa Bezerra de Menezes, R., Costa Martins, A.
21-04-2022
Chem Biol Interact
https://pubmed.ncbi.nlm.nih.gov/35461787

Chagas disease is a disease that is emerging in North America and Europe countries. Benznidazole is the main drug available, but it has high toxicity and low efficacy in the chronic phase. In this way, researching new antichagasic agents is necessary. Thus, the aim of this study is to evaluate the effect of novel chalcones and the influence of chlorine substitutions on Trypanosoma cruzi and host cells. Unsubstituted (1), 4-chlorine substituted (2) and 2,4-chlorine substituted (3) chalcones were synthesized by Claisen-Schmidt condensation, characterized, and electrical distribution was assessed by Density Fuctional Theory (DFT). The host cells toxicity (LLC-MK2) was performed by 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) reduction assay. The effect on epimastigote (24, 48 and 72h), trypomastigote (24h) and amastigotes (24 h) was evaluated. Flow cytometry assays were performed with 7-Aminoactinomycin D (7-AAD) and Annexin-PE, Dichlorofluorescein diaceteate (DCFH-DA) and Rhodamine123 (Rho123). Finally, molecular docking predicted interactions between chalcones and cruzain (TcCr) and trypanothione reductase (TcTR). The toxicity on host cells was reduced almost twenty times on chlorine substituted molecules. On epimastigote and trypomastigote forms, all substances presented similar effects. After treatment with molecule 3, it was observed a decrease in infected cells and intracellular amastigotes. Their effect is related to necrotic events, increase of cytoplasmic Reactive Oxygen Species (ROS) and mitochondrial dysfunction. Also, this effect might be associated with involvement of TcCr and TcTR enzymes. Therefore, the results showed that chlorine substitution on chalcones reduces the host cell's toxicity without compromising the effect on Trypanosoma cruzi Y strain forms, and it occurs over membrane damage, oxidative stress and possible interactions with TcCr and TcTR.

Population Pharmacokinetics of Nifurtimox in Adult and Pediatric Patients with Chagas' Disease.

Ince, I., Prins, K., Willmann, S., Sutter, G., Hanze, E., Sadre-Marandi, F., Stass, H., Garmann, D.
23-04-2022
J Clin Pharmacol
https://doi.org/10.1002/jcph.2064

Nifurtimox (LAMPIT®) has been used for decades for the treatment of Chagas' Disease, a chronic and potentially life-threatening disease caused by the parasite Trypanonosma Cruzi. The pharmacokinetics (PK) information on nifurtimox in humans derived from controlled clinical studies is very limited. The objective was to investigate and compare the Population PK (PopPK) of nifurtimox in adult and pediatric patients with Chagas' disease to confirm the clinical dosing regimen in children, which was based on allometric approaches using the concept that a dose equivalent exposure would reach equivalent antiparasitic efficacy as in adults. The resulting adult model adequately described the PK in adults. Significant predictors of the availability in PK were food intake, tablet formulation (fast vs. slow dissolution tablet), study, and body weight (WT). As the resulting adult model could not adequately predict the sparse sampled pediatric patient data, these data were analyzed separately to derive exposure estimates for comparison with adult exposure. In the PopPK model for pediatric patients, significant covariates were WT and age. As compared to adults, children older than 2 years were estimated to have 50.6 % higher apparent clearance (CL/F). No hints of dose-nonlinearity were observed in a dose range of 30 to 240 mg single dose in adults and 15 to 300 mg 3 times daily (8 to 20 mg/kg) in children. Altogether, this study retroactively showed that the current mg/kg dosing regimen in children reached similar exposure as in adults receiving an 8 mg/kg total daily dose. This article is protected by copyright. All rights reserved.

Atypical strategies for cuticle pigmentation in the blood-feeding hemipteran Rhodnius prolixus.

Berni, M., Lima, L., Bressan, D., Julio, A., Bonfim, L., Simão, Y., Pane, A., Ramos, I., Oliveira, P., Araujo, H.
21-04-2022
Genetics
https://pubmed.ncbi.nlm.nih.gov/35445704

Pigmentation in insects has been linked to mate selection and predator evasion, thus representing an important aspect for

natural selection. Insect body color is classically associated to the activity of tyrosine pathway enzymes, and eye color to pigment synthesis through the tryptophan and guanine pathways, and their transport by ABC proteins. Among the hemiptera, the genetic basis for pigmentation in kissing bugs such as Rhodnius prolixus, that transmit Chagas disease to humans, has not been addressed. Here we report the functional analysis of R. prolixus eye and cuticle pigmentation genes. Consistent with data for most insect clades, we show that knockdown for yellow results in a yellow cuticle, while scarlet and cinnabar knockdowns display red eyes as well as cuticle phenotypes. In addition, tyrosine pathway aaNATpreto knockdown resulted in a striking dark cuticle that displays no color pattern or UV reflectance. In contrast, knockdown of ebony and tan, that encode NBAD branch tyrosine pathway enzymes, did not generate the expected dark and light brown phenotypes, respectively, as reported for other insects. We hypothesize that R. prolixus, which requires tyrosine pathway enzymes for detoxification from the blood diet, evolved an unusual strategy for cuticle pigmentation based on the preferential use of a color erasing function of the aaNATpreto tyrosine pathway branch. We also show that genes classically involved in the generation and transport of eye pigments regulate red body color in R. prolixus. This is the first systematic approach to identify the genes responsible for the generation of color in a blood-feeding hemiptera, providing potential visible markers for future transgenesis.

A longitudinal two-year survey of the prevalence of trypanosomes in domestic cattle in Ghana by massively parallel sequencing of barcoded amplicons.

Ofori, J., Bakari, S., Bah, S., Kolugu, M., Aning, G., Awandare, G., Carrington, M., Gwira, T.
20-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010300

Background: Animal African Trypanosomiasis (AAT) is one of the most economically important diseases affecting livestock productivity in sub-Saharan Africa. The disease is caused by a broad range of Trypanosoma spp., infecting both wild and domesticated animals through cyclical and mechanical transmission. This study aimed to characterize trypanosomes present in cattle at regular intervals over two years in an AAT endemic and a non-endemic region of Ghana. Methodology/Principal findings: Groups of cattle at Accra and Adidome were selected based on their geographical location, tsetse fly density, prevalence of trypanosomiasis and the breed of cattle available. Blood for DNA extraction was collected at approximately four to five-week intervals over a two-year period. Trypanosome DNA were detected by a sensitive nested PCR targeting the tubulin gene array and massively parallel sequencing of barcoded amplicons. Analysis of the data was a semi-quantitative estimation of infection levels using read counts obtained from the sequencing as a proxy for infection levels. Majority of the cattle were infected with multiple species most of the time [190/259 (73%) at Adidome and 191/324 (59%) at Accra], with T. vivax being the most abundant. The level of infection and in particular T. vivax, was higher in Adidome, the location with a high density of tsetse flies. The infection level varied over the time course, the timings of this variation were not consistent and in Adidome it appeared to be independent of prophylactic treatment for trypanosome infection. Effect of gender or breed on infection levels was insignificant. Conclusions/Significance: Most cattle were infected with low levels of several trypanosome species at both study sites, with T. vivax being the most abundant. The measurements of infection over time provided insight to the importance of the approach in identifying cattle that could suppress trypanosome infection over an extended time and may serve as reservoir.

LEISHMANIOSE

Utilizing Quantitative Proteomics to Identify Species-Specific Protein Therapeutic Targets for the Treatment of Leishmaniasis.

Krobthong, S., Yingchutrakul, Y., Samutrtai, P., Hitakarun, A., Siripattanapipong, S., Leelayoova, S., Mungthin, M., Choowongkomon, K.
04-04-2022
ACS Omega
https://doi.org/10.1021/acsomega.1c05792

Leishmaniasis is a tropical disease caused by *Leishmania* parasites, which are transmitted through the bites of infected sandflies. We focused on the emergence of leishmaniasis in Thailand caused by a species (*Leishmania orientalis*). Treatment by chemotherapy is not effective against *L. orientalis*. Hence, we intended to solve this issue using a proteomics approach to investigate protein profiles and *in silico* analysis for the identification of antigenic proteins from *L. orientalis*, *Leishmania martiniquensis*, and *Leishmania donovani*. Using principal component analysis (PCA), protein profile comparisons indicated that different species of *Leishmania* are different at the protein level. Proteomics analysis identified 6099 proteins. Among these proteins, 1065 proteins were used for further analysis. There were 16 proteins that were promising candidates for therapeutic aspects as they were abundantly expressed and common to all species. *In silico* analysis of protein's antigenicity revealed that eight proteins had the potential for the development of antigenic molecules. Protein profile information and these antigenic proteins may play key roles in the pathogeny of leishmaniasis and can be used as novel therapeutic targets against leishmaniasis in the future.

FRB domain of human TOR protein induces compromised proliferation and mitochondrial dysfunction in Labrus donovani promastigotes.

Chakraborty, S., Mukherjee, S., Biswas, P., Ghosh, A., Siddhanta, A.
23-04-2022
Parasitol Int
https://pubmed.ncbi.nlm.nih.gov/35472440

Visceral leishmaniasis (VL) or Kala-azar, the second-largest parasitic killer worldwide, is caused by Leishmania donovani. The drugs to treat VL are toxic and expensive. Moreover, their indiscriminate use gave rise to resistant strains. The high rate of parasite proliferation within the host macrophage cells causes pathogenesis. In the proliferative pathway, FRB domain of TOR protein is ubiquitously essential. Although orthologues of mTOR protein are reported in trypanosomatids and Leishmania but therein depth molecular characterization is yet to be done. Considerable protein sequence homology exists between the TOR of kinetoplastidas and mammals. Interestingly, exogenous human FRB domain was shown to block G1 to S transition in mammalian cancer cells. Thus, we hypothesized that expression of human FRB domain would inhibit the proliferation of Labrus donovani. Indeed, promastigotes stably expressing wild type human FRB domain show 4.7 and 1.5 folds less intra- and extra-cellular proliferations than that of untransfected controls. They also manifested 2.65 times lower rate of glucose stimulated oxygen consumption. The activities of all respiratory complexes were compromised in the hFRB expressing promastigotes. In these cells, depolarized mitochondria were 2-fold more than control cells. However, promastigotes expressing its mutant version (Trp^{2027}-Phe) has shown similar characteristics like untransfected cells. Thus, this study reveals greater insights on the conserved role of TOR in the regulation of the respiratory complexes in L. donovani. The slow growing variant of FRB expressing promastigotes will have great potential to be exploited as a prophylactic agent against leishmaniasis.

In silico and in vitro antileishmanial effects of gamma-terpinene: Multifunctional modes of action.

Nooshadokht, M., Mirzaei, M., Sharifi, I., Sharifi, F., Lashkari, M., Amirheidari, B.
23-04-2022
Chem Biol Interact
https://pubmed.ncbi.nlm.nih.gov/35472413

Introduction: Leishmaniasis denotes a significant health challenge worldwide with no ultimate treatment. The current study investigated the biological effects of gamma-terpinene (GT) on Leishmania major in putative antileishmanial action, cytotoxicity, apoptosis induction, gene expression alteration, antioxidant activity, hemolysis, and ROS generation. Methods: GT and meglumine antimoniate (MA) were probed alone and in combination (GT/MA) for their anti-leishmanial potentials using the MTT biochemical colorimetric assay and a model macrophage cell. In addition, their immunomodulatory properties were assessed by analyzing their effect on the transcription of cytokines related to Th1 and Th2 responses. GT and MA, alone and in combination, were also assessed for their potential to alter metacaspase gene expression in L. major promastigotes by real-time RT-PCR. The hemolytic potential of GT and MA-treated promastigotes were also measured by routine UV absorbance reading. Electrophoresis on agarose gel was employed to analyze genomic DNA fragmentation. Results: GT demonstrated notable dose-dependent antileishmanial effects towards promastigotes and amastigotes of L. major. The IC_{50} values for GT against L. major promastigotes and amastigotes were 46.76 mM and 25.89 mM, respectively. GT was considerably safer towards murine macrophages than L. major amastigotes with an SI value of 3.17. Transcriptional expression of iNOS, JAK-1, Interleukin (IL-10), and TGF-β was meaningfully decreased, while the levels of metacaspase mRNA were increased. Results also confirmed GT antioxidant activities. Also, increased levels of intracellular ROS were observed upon treatment of promastigotes with GT. The gel electrophoresis result indicated slight DNA fragmentation in the treated promastigotes by both drugs. A weak hemolytic effect was also observed for GT. Conclusion: The results demonstrated that GT showed potent activity against L. major stages. It seems that its mechanism of action involves representing an immunomodulatory role towards upregulation of iNOS and JAK-1, while downregulation of IL-10 and TGF- β. Moreover, GT has an antioxidative potential and exerts its action through activating macrophages to kill the organism. Further in vivo and clinical studies are essential to explore its effect in future programs.

Advances in the management of Acanthamoeba keratitis: A review of the literature and synthesized algorithmic approach.

Kaufman, A., Tu, E.
21-04-2022
Ocul Surf
https://pubmed.ncbi.nlm.nih.gov/35462076

Acanthamoeba keratitis (AK) is a severe cause of infectious keratitis and presents a significant clinical challenge. Recent literature regarding AK epidemiology, diagnosis, treatment modalities, and prognosis is reviewed and synthesized to propose an algorithmic protocol for AK management. Globally, AK outbreaks in developed countries are ongoing, and AK rates have increased. Moreover, current outbreaks may carry a worse prognosis than prior outbreaks. Despite identification of contact lens solutions implicated in AK outbreaks and the consequent market recall of these products, outbreaks persist. Acanthamoeba keratitis afflicts not only refractive soft contact lens users but also cosmetic contact lens users and gas permeable (especially orthokeratology) lens users. Innovations in in vivo confocal microscopy and PCR assays have increased the role for these adjuvant tests alongside corneal smear and culture in a multimodal diagnostic approach to suspected AK. Biguanides (such as chlorhexidine and polyhexamethylene biguanide) and diamidines (propamidine isethionate and

hexamidine) remain cornerstones of AK management, and evidence for other treatment modalities continues to evolve. Voriconazole in topical and systemic forms may be useful in adjuvant therapy. The anti-leishmaniasis drug miltefosine, recently given orphan drug status by the United States Food and Drug Administration, has increasing evidence supporting its role in patients with severe/refractory disease. Prior topical corticosteroids have been consistently shown to be associated with worse outcomes in AK. Although not historically thought of as a treatment modality, benzalkonium chloride preservative may be leveraged for its anti-Acanthamoebal properties. The role of Rose-Bengal photodynamic antimicrobial therapy is evolving in selected cases of AK.

Unsaturated lipids modulating the interaction of the antileishmanial isolinderanolide E with models of cellular membranes.

Rosa, M., Alves Conserva, G., Passero, L., Lago, J., Caseli, L.
18-04-2022
Bioorg Chem
https://pubmed.ncbi.nlm.nih.gov/35461015

The present work evaluated the antiprotozoal activity of isolinderanolide E, isolated from the Brazilian plant Nectandra oppositifolia, against promastigote forms of Leishmania (Leishmania) amazonensis. The compound exhibited an EC_{50} value of 20.3 µM, similar to the positive control miltefosine (IC_{50} of 19.4 µM), and reduced toxicity to macrophages (CC_{50} > 200 µM). Based on these results, Langmuir monolayers of two unsaturated lipids: 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) and 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), were employed as a model of mammalian and parasite membranes, respectively, to study the interaction of isolinderanolide E at a molecular level. The films were characterized with tensiometry (surface pressure-area isotherms and surface pressure-time curves), infrared spectroscopy, and Brewster angle microscopy (BAM). This compound changed the profile of the isotherms leading to fluid DOPC and DOPE monolayers, which were not able to attain rigid states even with compression. Infrared spectroscopy showed that the bioactive compound decreases the trans/gauche ratio conformers related to the molecular conformational disorder. BAM showed the formation of specific aggregates upon drug incorporation. In conclusion, isolinderanolide E changes the thermodynamic, mechanical, structural, and morphological characteristics of the monolayer of these unsaturated lipids, which may be essential to understand the action at the molecular level bioactives in biointerfaces.

Bionomics of the unexplored sand flies fauna of District Mohmand, Khyber Pakhtunkhwa, Pakistan: assessing risk factors associated with cutaneous leishmaniasis.

Khan, K., Sajjad, M., Wahid, S., Gul, M., Khan, L., Ullah, H., Rahman, Y., Khan, D., Khan, K., Khan, M., Khan, S., Shah, S.
23-04-2022
Trans R Soc Trop Med Hyg
https://pubmed.ncbi.nlm.nih.gov/35460562

Background: Sand flies are of considerable public health importance in Pakistan because these insects are vectors of leishmaniasis. The current study explores the bionomics of sand flies, their spatial distribution pattern and cutaneous leishmaniasis-associated risk factors in District Mohmand, Khyber Pakhtunkhwa, Pakistan. **Methods:** Sand flies were collected from indoor and outdoor habitats in 69 villages of five tehsils in Mohmand during July-October 2019. Risk factor data were recorded for 829 households in 94 villages. **Results:** In total, 2065 sand flies were captured. Phlebotomus (Paraphlebotbmus) sergenti was the most abundant species. Relative density for P. sergenti and Phlebotomus papatasi was highest in Prang Ghar and lowest in Safi. Sand flies abundance peaked in August and September, corresponding to maximum relative humidity, temperature and rainfall. Relative density for P. sergenti and P. papatasi was highest in combined dwellings (indoor) and cattle corrals (outdoor). Phlebotomus sergenti and P. papatasi were abundant at an elevation of 283-1140 m on agricultural land and rangelands. Both species were recorded abundantly on Carbontites, Mesozoic and Indus suture Melange rock formations. Presence of domestic animals, ownership of pet dogs, presence of muddy dunes in the village, knowledge of sandflies and use of mosquitoes spray remained significant risk factors. **Conclusions:** The study reports sand fly bionomics in District Mohmand. Risk identified for cutaneous leishmaniasis are significant in strategising control methods for Health authorities can allocate localized control means to high-risk areas using these findings.

Metamorphosis of neutrophil transcriptional programme during Leishmania infection.

Revue de littérature

DeSouza-Vieira, T.
19-04-2022
Parasite Immunol
https://doi.org/10.1111/pim.12922

The role of neutrophils in the course of Leishmania infection remains controversial, displaying tremendous variability depending on the species of parasite, stage of infection, host genetic background, and methodological discrepancies among studies. Although neutrophils have long been categorized as short-lived cells with limited capacity to express proteins de novo, recent advances have revealed significant plasticity in neutrophil transcriptional programmes and intrapopulation heterogeneity, which can be regulated by both intrinsic and extrinsic factors that together determine the profile of neutrophil effector response. In this review, we focus on the current understanding of neutrophil transcriptional plasticity, neutrotime, evidence of Leishmania-mediated alterations in neutrophil transcriptome leading to the rise of subpopulations, and finally, functional implications of those findings to the course of Leishmania infection.

CYSTICERCOSE

DRACUNCULOSE

ECHINOCOCCOSE

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

FILARIOSE LYMPHATIQUE

MYCETOME

ONCHOCERCOSE

Anti-Th17 and anti-Th2 responses effects of hydro-ethanolic extracts of Aframomum melegueta, Khaya senegalensis and Xylopia aethiopica in hyperreactive onchocerciasis individuals' peripheral blood mononuclear cells.

Katawa, G., Ataba, E., Ritter, M., Amessoudji, O., Awesso, E., Tchadié, P., Bara, F., Douti, F., Arndts, K., Tchacondo, T., Batawila, K., Ameyapoh, Y., Hoerauf, A., Karou, S., Layland, L.
25-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010341

Hyperreactive onchocerciasis (HO) is characterized by a severe skin inflammation with elevated Th17-Th2 combined responses. We previously demonstrated the anthelminthic activity of Aframomum melegueta (AM), Xylopia aethiopica (XA) and Khaya senegalensis (KS) used by traditional healers to treat helminthiasis in the endemic area of Togo. However, their effect on severe onchocerciasis is poorly investigated. The present study aimed to investigate the anti-Th17 and anti-Th2 effects of hydro-ethanolic extracts of AM, XA and KS during HO. Onchocerca volvulus-infected individuals were recruited in the Central region of Togo in 2018. Isolated peripheral blood mononuclear cells (PBMCs) from both generalized onchocerciasis (GEO) and HO forms were activated with anti-CD3 and anti-CD28 monoclonal antibodies in the presence or absence of the hydro-ethanolic extracts of AM, XA and KS as well as their delipidated, deproteinized and deglycosylated fractions. After 72 hours, cytokines were assayed from cell culture supernatants. Then, flow cytometry was used to investigate the effects of the extracts on cell activation, proliferation, intracellular cytokines and T cells transcription factors. The production of both Th17 and Th2 cytokines IL-17A and IL-5 were significantly inhibited upon T-cell receptor (TCR) activation in the presence of the hydro-ethanolic extracts of AM, XA and KS in HO individuals' PBMCs in vitro. AM and XA inhibited CD4+RORC2+IL-17A+ and CD4+GATA3+IL-4+ cell populations induction. This inhibition was not Th1 nor Treg-dependent since both IFN-γ and IL-10 were also inhibited by the extracts. AM and XA did not interfere with T cell activation and proliferation for their inhibitory pathways. Lipid and protein compounds from AM and XA were associated with the inhibition of IL-17A. This study showed that in addition to their anthelminthic effects, hydro-ethanolic extracts of Aframomum melegueta, Xylopia aethiopica and Khaya senegalensis could downregulate both Th17 and Th2 responses and prevent the severe skin disorder observed.

Genetic and geographical delineation of zoonotic vector-borne helminths of canids.

Laidoudi, Y., Bedjaoui, S., Latrofa, M., Fanelli, A., Dantas-Torres, F., Otranto, D.
24-04-2022
Sci Rep
https://doi.org/10.1038/s41598-022-10553-w

Several zoonotic vector-borne helminths (VBHs) infesting canids cause serious veterinary and medical diseases worldwide. Increasing the knowledge about their genetic structures is pivotal to identify them and therefore to settle effective surveillance and control measures. To overcome the limitation due to the heterogeneity of large DNA sequence-datasets used for their genetic characterization, available cytochrome c oxidase subunit 1 (cox1) (n=546) and the 12S rRNA (n=280) sequences were examined using combined bioinformatic approach (i.e., distance-clustering, maximum likelihood phylogeny and phylogenetic evolutionary placement). Out of the 826 DNA available sequences from GenBank, 94.7% were characterized at the haplotype level regardless sequence size, completeness and/or their position. A total of 89 different haplotypes were delineated either by cox1 (n=35), 12S rRNA (n=21) or by both genes (n=33), for 14 VBHs (e.g., Acanthocheilonema reconditum, Brugia spp., Dirofilaria immitis, Dirofilaria repens, Onchocerca lupi and Thelazia spp.). Overall, the present approach could be useful for studying global genetic diversity and phylogeography of

VBHs. However, as barcoding sequences were restricted to two mitochondrial loci (cox1 and 12S rRNA), the haplotype delineation proposed herein should be confirmed by the characterization of other nuclear loci also to overcome potential limitations caused by the heteroplasmy phenomenon within the mitogenome of VBHs.

SCHISTOSOMIASE

Infection intensity-dependent accuracy of reagent strip for the diagnosis of Schistosoma haematobium and estimation of treatment prevalence thresholds.

Grolimund, C., Bärenbold, O., Hatz, C., Vennervald, B., Mayombana, C., Mshinda, H., Utzinger, J., Vounatsou, P.
25-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010332

Background: Reagent strip to detect microhematuria as a proxy for Schistosoma haematobium infections has been considered an alternative to urine filtration for individual diagnosis and community-based estimates of treatment needs for preventive chemotherapy. However, the diagnostic accuracy of reagent strip needs further investigation, particularly at low infection intensity levels. Methods: We used existing data from a study conducted in Tanzania that employed urine filtration and reagent strip testing for S. haematobium in two villages, including a baseline and six follow-up surveys after praziquantel treatment representing a wide range of infection prevalence. We developed a Bayesian model linking individual S. haematobium egg count data based on urine filtration to reagent strip binary test results available on multiple days and estimated the relation between infection intensity and sensitivity of reagent strip. Furthermore, we simulated data from 3,000 hypothetical populations with varying mean infection intensity to infer on the relation between prevalence observed by urine filtration and the interpretation of reagent strip readings. Principal findings: Reagent strip showed excellent sensitivity even for single measurement reaching 100% at around 15 eggs of S. haematobium per 10 ml of urine when traces on reagent strip were considered positive. The corresponding specificity was 97%. When traces were considered negative, the diagnostic accuracy of the reagent strip was equivalent to urine filtration data obtained on a single day. A 10% and 50% urine filtration prevalence based on a single day sampling corresponds to 11.2% and 48.6% prevalence by reagent strip, respectively, when traces were considered negative, and 17.6% and 57.7%, respectively, when traces were considered positive. Conclusions/Significance: Trace results should be included in reagent strip readings when high sensitivity is required, but excluded when high specificity is needed. The observed prevalence of reagent strip results, when traces are considered negative, is a good proxy for prevalence estimates of S. haematobium infection by urine filtration on a single day.

Inhibition of COX-2 ameliorates murine liver schistosomiasis japonica through splenic cellular immunoregulation.

Qi, Z., Lan, C., Xiaofang, J., Juanjuan, T., Cheng, F., Ting, H., Erxia, S., Zi, L.
23-04-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05201-1

Background: We have reported the positive association of the cyclooxygenase 2 (COX-2)/prostaglandin E2 (PGE2) axis with liver fibrosis induced by Schistosoma japonicum (Sj) infection, and TLR4 signaling controlled this axis. However, how COX-2 regulates immune response during Sj infection is still unclear. Methods: Hematoxylin and eosin staining was used to evaluate the effect of the COX-2-specific inhibitor NS398 on liver granulomatous inflammation and fibrosis. Flow cytometry was used to explore the frequency and amount of different immune cell infiltration in the spleen during Sj infection. Results: NS398 significantly reduced the size of liver granuloma, spleen, and mesenteric lymph node (MLN) and alleviated chronic granulomatous inflammation. Mechanically, this might be by decreasing the number of Sj-induced macrophages and T helper type 1 (Th1), Th2, T follicular helper (Tfh), T follicular regulatory (Tfr), and germinal center B (GC B) cells. There were no differences in the number of neutrophils, myeloid-derived suppressor cells, Th17 cells, regulatory T cells (Treg), or total B cells in the spleen of the mice with or without NS398 treatment. Conclusions: COX-2/PGE2 inhibition may represent a potential therapeutic approach for schistosomiasis japonica through splenic cellular immunoregulation.

Gallbladder schistosomiasis displaying as gallbladder perforation: A case report.

Wang, B., Jin, C., Gu, Y.
19-04-2022
Asian J Surg
https://pubmed.ncbi.nlm.nih.gov/35459593

Schistosomicidal and hepatoprotective activity of gamma-aminobutyric acid (GABA) alone or combined with praziquantel against Schistosoma mansoni infection in murine model.

Fahmy, A., William, S., Hegab, A., Tm, D.
18-04-2022
Exp Parasitol
https://pubmed.ncbi.nlm.nih.gov/35447136

Objective: This study aimed to evaluate the efficacy of gamma-aminobutyric acid (GABA) alone or combined with praziquantel (PZQ) against Schistosoma (S) mansoni infection in a murine model. Methods: Five groups, 8 mice each, were studied; GI served as normal controls; GII: S. mansoni-infected

control group and the other three S. mansoni-infected groups received drug regimens for 5 consecutive days as follows GIII: Infected-PZQ treated group (200 mg/kg/day); GIV: Infected-GABA treated group (300 mg/kg/day) and GV: Infected-PZQ-GABA treated group (100 mg/kg/day for each drug). All animal groups were sacrificed two weeks later and different parasitological, histopathological and biochemical parameters were assessed. **Results:** Combined GABA-PZQ treated group recorded the highest significant reduction in all parasitological, histopathological and biochemical parameters followed by PZQ and finally GABA groups. Combined GABA-PZQ treatment led to the complete disappearance of immature eggs and marked reduction of deposited eggs in liver tissues and improved liver pathology. Significant improvement in hepatic oxidative stress levels, serum albumin and total protein in response to GABA treatment alone or combined with PZQ. **Conclusion:** GABA had schistosomicidal, hepatoprotective and antioxidant activities against S. mansoni infection, GABA disrupted parasite pairing and activity, reduced the total number of worms recovered and the number of ova in the tissues. GABA may be considered an adjuvant therapy to potentiate PZQ antiparasitic activity and eradicate infection-induced liver damage and oxidative stress.

Pathological and immunological evaluation of different regimens of praziquantel treatment in a mouse model of Schistosoma mansoni infection.

Membe Femoe, U., Boukeng Jatsa, H., Greigert, V., Brunet, J., Cannet, C., Kenfack, M., Gipwe Feussom, N., Kadji Fassi, J., Tienga Nkondo, E., Abou-Bacar, A., Pfaff, A., Dimo, T., Kamtchouing, P., Tchuem Tchuenté, L.
21-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010382

Background: One of the considerable challenges of schistosomiasis chemotherapy is the inefficacy of praziquantel (PZQ) at the initial phase of the infection. Immature schistosomes are not susceptible to PZQ at the curative dose. Here, we investigated the efficacy of different PZQ regimens administered during the initial stage of Schistosoma mansoni infection in mice. **Methodology/Principal findings:** Two months-old mice were individually infected with 80 S. mansoni cercariae and divided into one infected-untreated control group (IC) and four PZQ-treated groups: PZQ at 100 mg/kg/day for five consecutive days (group PZQ1), PZQ at 100 mg/kg/day for 28 days (group PZQ2), PZQ at 18 mg/kg/day for 28 days (group PZQ3) and a single dose of PZQ at 500 mg/kg (group PZQ4). The treatment started on day one post-infection (p.i), and each group of mice was divided into two subgroups euthanized on day 36 or 56 p.i, respectively. We determined the mortality rate, the parasitological burden, the hepatic and intestinal granulomas, the serum levels of Th-1, Th-2, and Th-17 cytokines, and gene expression. The treatment led to a significant ($p < 0.001$) reduction of worm burden and egg counts in the intestine and liver in groups PZQ2 and PZQ3. On 56th day p.i, there was a significant reduction ($p < 0.001$) of the number and volume of the hepatic granulomas in groups PZQ2 and PZQ3 compared to group PZQ1 or PZQ4. Moreover, in group PZQ3, the serum levels of IFN-γ, TNF-α, IL-13, and IL-17 and their liver mRNA expressions were significantly reduced while IL-10 and TGF-β gene expression significantly increased. The highest mortality rate (81.25%) was recorded in group PZQ2. **Conclusion/Significance:** This study revealed that the administration of PZQ at 18 mg/kg/day for 28 consecutive days was the optimal effective posology for treating S. mansoni infection at the initial stage in a murine model.

Susceptibility of embryos of Biomphalaria tenagophila (Mollusca: Gastropoda) to infection by Pochonia chlamydosporia (Ascomycota: Sordariomycetes).

Castro, L., Martins, I., Tunholi-Alves, V., Amaral, L., Pinheiro, J., de Araújo, J., de Oliveira Monteiro, C., Tunholi, V.
20-04-2022
Arch Microbiol
https://doi.org/10.1007/s00203-022-02894-x

Schistosoma mansoni is a heteroxenous parasite, meaning that during its life cycle needs the participation of obligatory intermediate and definitive hosts. The larval development occurs in aquatic molluscs belonging to the Biomphalaria genus, leading to the formation of cercariae, which emerge to infect the final vertebrate host. For this reason, studies for control of the diseases caused by digenetic trematodes often focus on combating the snail hosts. Thus, the objective of this study was to evaluate the susceptibility of Biomphalaria tenagophila embryos to the fungus Pochonia chlamydosporia (isolate Pc-10). The entire experiment was conducted in duplicate, with five replicates for each repetition (five egg masses/replicate), utilizing a total of 100 egg masses, with 20-30 eggs/egg mass. At the end of 15 days, the egg masses were evaluated under a stereomicroscope to analyze the hatching of B. tenagophila embryos in both experimental groups. After days of interaction, the exposure to the fungal hyphae bodies significantly impaired the viability of the B. tenagophila eggs, inhibiting the embryogenesis process by 83.7% in relation to the control group. Transmission and scanning electron microscopic images revealed relevant structural alterations in the egg masses exposed to the hyphae action of the fungus, interfering in the development and hatching of the young snails under analysis. These results indicate the susceptibility of B. tenagophila embryos to the fungus P. chlamydosporia (isolate Pc-10) and suggest the potential of Pc-10 to be used in the control of intermediate host, for its ovicidal capacity and for being an ecologically viable option, but in vivo experiments become necessary.

Prevalence and risk factors of urogenital schistosomiasis among under-fives in Mtama District in the Lindi region of Tanzania.

Mushi, V., Zacharia, A., Shao, M., Mubi, M., Tarimo, D.
20-04-2022
PLoS Negl Trop Dis

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Introduction: Despite the ongoing intervention for schistosomiasis control among school-age children in the Lindi region of Tanzania, urogenital schistosomiasis continues to be a public health problem, presumably because other at-risk populations are not covered in praziquantel deworming campaigns. Evidence shows that under-fives become infected in their early life hence the need to understand the disease profile and the risk factors for exposure to infection so as to plan effective control strategies in this group. This study examined the prevalence and risk factors of urogenital schistosomiasis among under-fives in the Mtama district, Lindi region of Tanzania. **Methodology/Principal findings:** A quantitative community-based cross-sectional study was carried out among 770 participants (385 under-fives and their 385 parents/guardians) in the Mtama district to investigate the burden and the risk factors associated with S. haematobium infection. A single urine specimen was collected from the under-fives and tested for macro and microhaematuria, presence of S. haematobium ova, and intensity of infection. A structured questionnaire gathered on risk factors for S. haematobium exposure in under-fives from their parents/guardians. Data analysis was performed using descriptive statistics, chi-square test, and logistic regression. Prevalence of S. haematobium ova was 16.9%, and that of macro and microhaematuria was 6% and 17.9%, respectively. Of the 65 positive under-fives, 49 (75.4%) 95% CI 65.4-86.3 had a light infection intensity, and 16 (24.6%) 95% CI 13.7-35.5 had a heavy infection intensity. Among the assessed risk factors, the parents/guardians habit of visiting water bodies for domestic routines (AOR: 1.44, 95% CI: 1.13-1.74), especially the river (AOR: 6.00, 95% CI: 1.20-35.12), was found to be a significant risk factor for infection of S. haematobium in under-fives. **Conclusion/Significance:** A moderate prevalence of S. haematobium was found among the under-fives conceivably with adverse health events. The infected under-fives could be a source of continuity for transmission in the community. An intervention that covers this group is necessary and should be complemented with regular screening, health education campaigns, and an adequate supply of safe water.

An assessment of implementation and effectiveness of mass drug administration for prevention and control of schistosomiasis and soil-transmitted helminths in selected southern Malawi districts.

Makaula, P., Kayuni, S., Mamba, K., Bongololo, G., Funsanani, M., Musaya, J., Juziwelo, L., Furu, P.

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Background: Mass drug administration (MDA) is one of the key interventions recommended by WHO for prevention and control of neglected tropical diseases (NTD). In Malawi, MDA is widely carried out annually since 2009 for prevention and control of schistosomiasis and soil-transmitted helminths (STH). No study has been carried out to assess effectiveness of the MDA approach and to document perceptions of health providers and beneficiaries regarding use of MDA. This study was done to understand how well MDA is being implemented and to identify opportunities for improvement in MDA delivery in Malawi. **Methods:** Designed as a cross-sectional and multi-methods research, the study was carried out in three southern Malawi districts of Chiradzulu, Mangochi and Zomba. In each district, four health centres and 16 villages were randomly selected to participate. A mixed-methods approach to data collection focusing on quantitative data for coverage and knowledge, attitudes and practices assessments; and qualitative data for assessing perceptions of health providers and beneficiaries regarding MDA was used. Quantitative data were processed and analyzed using IBM SPSS software version 26 while qualitative data were analysed using NVivo 12 for Windows. **Results:** Knowledge levels about schistosomiasis and STH in the districts varied according to disease aspects asked about. Majority are more knowledgeable about what schistosomiasis is (78%) and whether STH are treatable with drugs (97%); with least knowledgeable about the organism that transmits schistosomiasis (18%), types of schistosomiasis (11%) and what causes STH (20%). In 2018 and 2019 the districts registered high coverage rates for praziquantel and albendazole using community-based MDA (73-100%) and using school-based MDA (75-91%). Both the health authorities and community members perceived the MDA approach as good because it brings treatment closer to people. **Conclusion:** With the high MDA coverage obtained in communities and schools, the effectiveness of MDA in the target districts is satisfactory. There are, however, several challenges including disproportionate knowledge levels, which are hampering progress towards attainment of the 2030 global NTD goals. There is a need for promotion of community participation and partnerships as well as implementation of other recommended interventions for sustainable prevention and control of schistosomiasis and STH.

Screening of a Library of Recombinant Schistosoma mansoni Proteins With Sera From Murine and Human Controlled Infections Identifies Early Serological Markers.

Crosnier, C., Hokke, C., Protasio, A., Brandt, C., Rinaldi, G., Langenberg, M., Clare, S., Janse, J., Wilson, S., Berriman, M., Roestenberg, M., Wright, G.

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Background: Schistosomiasis is a major global health problem caused by blood-dwelling parasitic worms, which is currently tackled primarily by mass administration of the drug praziquantel. Appropriate drug treatment strategies are informed by diagnostics that establish the prevalence and intensity of infection, which, in regions of low transmission, should be highly sensitive. **Methods:** To identify sensitive new serological markers of Schistosoma mansoni infections, we

have compiled a recombinant protein library of parasite cell-surface and secreted proteins expressed in mammalian cells. **Results:** Together with a time series of sera samples from volunteers experimentally infected with a defined number of male parasites, we probed this protein library to identify several markers that can detect primary infections with as low as 10 parasites and as early as 5 weeks postinfection. **Conclusions:** These new markers could be further explored as valuable tools to detect ongoing and previous S mansoni infections, including in endemic regions where transmission is low.

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

GALE

Biocontrol Effect of *Bacillus subtilis* YPS-32 on Potato Common Scab and Its Complete Genome Sequence Analysis.

Zhou, Y., Li, Q., Peng, Z., Zhang, J., Li, J.
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Potato common scab is caused by *Streptomyces*, which resides in soil and has become a serious disease in potato planting areas worldwide. In this study, we obtained a *Bacillus subtilis* YPS-32 strain by natural screening, and atmospheric and room-temperature plasma (ARTP) mutagenesis and field trial results showed that *B. subtilis* YPS-32 has a control efficacy of 83.70% against potato common scab. The complete genome of *B. subtilis* YPS-32 was sequenced, and multiple genes related to the synthesis of antibiotics and plant growth promoters were detected. Based on the genomic information for *B. subtilis* YPS-32, the *sfp* gene-inactivated (related to the synthesis of secondary metabolites) mutant strain *B. subtilis* YPS-32Δ*sfp* was constructed. Analysis of crude extract metabolites using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) and liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) techniques revealed that strain YPS-32 encodes antagonists, such as surfactin and fengycin, which have antimicrobial effects. This study clarifies the mode of action by which *B. subtilis* YPS-32 antagonizes *Streptomyces scabies* and provides a reference for further research on antibacterial genes in the future.

MORSURES DE SERPENT