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DENGUE, CHIKUNGUNYA ET MALADIE A VIRUS ZIKA

Cost-effectiveness of a Dengue Vector Control Intervention in Colombia.

Taborda, A., Chamorro, C., Quintero, J., Carrasquilla, G., Londoño, D.
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Dengue is a public health problem in Colombia and in the municipality of Girardot, an area of high risk for dengue transmission. We present the results of an economic evaluation from the societal perspective and 1-year time horizon comparing the regular control program for dengue prevention versus an intervention that comprised an environmental management strategy by covering the most Aedes aegypti productive breeding sites with insecticide covers, community actions, and educational activities. The effectiveness of the intervention was measured as the reduction in probability of dengue infection obtained from a community trial. Resource use was estimated from clinical records that were validated by clinical experts; unit costs were taken from national tariffs. Patient costs were obtained from a household survey. We found that the intervention generated an additional cost of USD20.9 per household and an incremental effectiveness of 0.00173 (reduction in the probability of reported dengue cases). Overall, both alternatives generate similar effectiveness, but the new intervention was associated with increasing costs. We conclude the new intervention is a potentially cost-effective option in areas where high prevalence of dengue exists.

"One feels anger to know there is no one to help us!". Perceptions of mothers of children with Zika virus-associated microcephaly in Caribbean Colombia: A qualitative study.

Marbán-Castro, E., Enguita-Fernàndez, C., Romero-Acosta, K., Arrieta, G., Marín-Cos, A., Mattar, S., Menéndez, C., Maixenchs, M., Bardají, A.
18-04-2022
PLoS Negl Trop Dis
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The epidemic of Zika virus (ZIKV) was associated with a sudden and unprecedented increase in infants born with microcephaly. Colombia was the second most affected country by the epidemic in the Americas. Primary caregivers of children with ZIKV-associated microcephaly, their mothers mainly, were at higher risk of suffering anxiety and depression. Often, these women were stigmatized and abandoned by their partners, relatives, and communities. This study aimed to understand the perceptions about ZIKV infection among mothers of children born with microcephaly during the ZIKV epidemic in Caribbean Colombia, and the barriers and facilitators affecting child health follow-up. An exploratory qualitative study, based on Phenomenology and Grounded Theory, was conducted in Caribbean Colombia. Data were collected through In-Depth Interviews (IDI) from women who delivered a baby with microcephaly during the ZIKV epidemic at Clínica Salud Social, Sincelejo, Sucre District (N = 11). The themes that emerged during the interviews included experiences from their lives before pregnancy; knowledge about ZIKV; experiences and perceptions when diagnosed; considering a possible termination of pregnancy, and children's clinical follow-up. In some cases, women reported having been told they were having a baby with microcephaly but decided not to terminate the pregnancy; while in other cases, women found out about their newborn's microcephaly condition only at birth. The main barriers encountered by participants during children's follow-up included the lack of psychosocial and economic support, the stigmatization and abandonment by some partners and relatives, and the frustration of seeing the impaired development of their children. This study contributed to identifying the social, medical, psychological, and economic needs of families with children affected by the ZIKV epidemic. Commitment and action by local and national governments, and international bodies, is required to ensure sustained and quality health services by affected children and their families.

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
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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.

Climate and visitors as the influencing factors of dengue fever in Badung District of Bali, Indonesia.

Maulana, M., Yudhastuti, R., Lusno, M., Mirasa, Y., Haksama, S., Husnina, Z.
18-04-2022
Int J Environ Health Res
https://doi.org/10.1080/09603123.2022.2065249

Badung district has recorded the highest dengue fever (DF) in Bali Province. This research presents the distribution of DF in Badung district and analyses its association with climate and visitors. The monthly data of DF, climate and number of visitors during January 2013 to December 2017 were analysed using Poisson Regression. A total of 10,689 new DF cases were notified from January 2013 to December 2017. DF in 2016 was recorded as the heaviest incidence. Monthly DF cases have positive association with average temperature (0.59 (95% CI: 0.56-.62)), precipitation (5.7×10^{-4} (95% CI: 3.8×10^{-4} - 7.6×10^{-4})), humidity (.014 (95% CI: 0.003-.025)) and local visitors (7.40×10^{-6} 95% CI: 5.88×10^{-6} : 8.91×10^{-6}). Negative association was shown between DF cases with foreign visitors (-2.18×10^{-6} (95% CI: -2.50×10^{-6} : -1.87×10^{-6})). This study underlines the urgency to integrate climate and tourism for DF surveillance.

Text Mining in Mosquito-Borne Disease: A Systematic Review.

Revue de littérature

Ong, S., Pauzi, M., Gan, K.
14-04-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35430265

Mosquito-borne diseases are emerging and re-emerging across the globe, especially after the COVID19 pandemic. The recent advances in text mining in infectious diseases hold the potential of providing timely access to explicit and implicit associations among information in the text. In the past few years, the availability of online text data in the form of unstructured or semi-structured text with rich content of information from this domain enables many studies to provide solutions in this area, e.g., disease-related knowledge discovery, disease surveillance, early detection system, etc. However, a recent review of text mining in the domain of mosquito-borne disease was not available to the best of our knowledge. In this review, we survey the recent works in the text mining techniques used in combating mosquito-borne diseases. We highlight the corpus sources, technologies, applications, and the challenges faced by the studies, followed by the possible future directions that can be taken further in this domain. We present a bibliometric analysis of the 294 scientific articles that have been published in Scopus and PubMed in the domain of text mining in mosquito-borne diseases, from the year 2016 to 2021. The papers were further filtered and reviewed based on the techniques used to analyze the text related to mosquito-borne diseases. Based on the corpus of 158 selected articles, we found 27 of the articles were relevant and used text mining in mosquito-borne diseases. These articles covered the majority of Zika (38.70%), Dengue (32.26%), and Malaria (29.03%), with extremely low numbers or none of the other crucial mosquito-borne diseases like chikungunya, yellow fever, West Nile fever. Twitter was the dominant corpus resource to perform text mining in mosquito-borne diseases, followed by PubMed and LexisNexis databases. Sentiment analysis was the most popular technique of text mining to understand the discourse of the disease and followed by information extraction, which dependency relation and co-occurrence-based approach to extract relations and events. Surveillance was the main usage of most of the reviewed studies and followed by treatment, which focused on the drug-disease or symptom-disease association. The advance in text mining could improve the management of mosquito-borne diseases. However, the technique and application posed many limitations and challenges, including biases like user authentication and language, real-world implementation, etc. We discussed the future direction which can be useful to expand this area and domain. This review paper contributes mainly as a library for text mining in mosquito-borne diseases and could further explore the system for other neglected diseases.

Anti-arboviral activity and chemical characterization of hispidulin and ethanolic extracts from *Millingtonia hortensis* L.f. and *Oroxylum indicum* (L.) Kurz (Bignoniaceae).

Cardoso Reis, A., Valente, G., Silva, B., de Brito Magalhães, C., Kohlhoff, M., Brandão, G.
15-04-2022
Nat Prod Res
https://doi.org/10.1080/14786419.2022.2065485

Millingtonia hortensis L.f. and *Oroxylum indicum* (L.) Kurz (Bignoniaceae) are native species from the Asian continent. They are popularly used in traditional medicine and their extracts are rich in flavonoids. In this work, ethanolic extracts of stems and leaves of these species were evaluated against the Chikungunya, Zika and Mayaro virus. The extracts were subjected to analysis by ultra-efficient liquid chromatography coupled to mass spectrometry. Additionally, *M. hortensis* leaves extract was fractionated, leading to the isolation of hispidulin. Anti-arboviral activity against the three viruses was detected for *M. hortensis* leaves extract with EC_{50} ranging

from 37.8 to 134.1 µg/mL and for *O. indicum* stems extract with EC_{50} ranging from 18.6 to 55.9 µg/mL. Hispidulin inhibited viral cytopathic effect of MAYV (EC_{50} value 32.2 µM) and CHIKV (EC_{50} value 78.8 µM). In LC-DAD-ESI-MS/MS analysis we characterized 25 flavonoids confirming once again the presence of these substances in extracts of these species.

Anti-viral activity of thiazole derivatives: an updated patent review.

Farghaly, T., Alsaedi, A., Alenazi, N., Harras, M.
15-04-2022
Expert Opin Ther Pat
https://doi.org/10.1080/13543776.2022.2067477

: Several viral infections cause life-threatening consequences in humans, making them the most serious worldwide public health concerns. Despite the fact that several antiviral medicines are available on the market, there is no full treatment for many important viral infections. To date, antiviral medicines have significantly reduced the spread of epidemics, but their continued use has resulted in the creation of drug-resistant variants throughout time. As a result, the development of new, safe, and efficient antiviral drugs for viral infections treatment is critical. : This review covered reports in the patent literature in the period 2014 to the first quarter of 2021 on the antiviral activities of thiazole derivatives. These molecules were reported to inhibit a wide range of viruses including influenza viruses, coronaviruses, herpes viruses, hepatitis B and C, bovine viral diarrhea virus, chikungunya virus and human immunodeficiency viruses. : the most bioactive molecules can be used as lead structures for the synthesis and development of new thiazole compounds with potent and selective antiviral activity. In addition, more efforts are needed to better understand the host-virus interactions for the discovery and development of new therapeutic agents and creative treatment strategies that are supposed to improve rates of clinical cure of the serious viruses.

Diagnosis of congenital infections in premature, low-birthweight newborns with intrauterine growth restriction caused by cytomegalovirus (CMV), herpes simplex virus (HSV), Parvo-B 19, and Zika virus: a systematic review.

Lino, J., Diniz, L., Rezende, L., Costa, V., Romanelli, R.
18-04-2022
J Perinat Med
https://doi.org/10.1515/jpm-2021-0244

To identify the prevalence of viral congenital infections in newborns classified as premature, low-birthweight, small for gestational age or intrauterine growth restriction. The definition considered for selecting papers were: P as newborns younger than 28 days; V as low-birthweight, prematurity and intrauterine growth restriction; O as frequency of congenital infections with Cytomegalovirus, Parvovirus B19, Herpes Simplex, and Zika virus. The research was performed using EMBASE, LILACS, SCOPUS and MEDLINE databases, with no limitations on date and language. Eight studies were included. Manuscripts including Herpes Simplex, Zika virus or Parvovirus B19 did not fulfill the defined criteria. A wide variation in the frequency of CMV congenital infection (0-4.8%) was found, which might be attributed to regional and methodological differences between investigations. Newborn characteristics associated with CMV congenital infections may direct investigations towards these patients with a higher probability of infection. However, as data are controversial, studies concerning screening of infection are important to define recommendations of diagnosis.

Risk and predictive factors for severe dengue infection: A systematic review and meta-analysis.

Yuan, K., Chen, Y., Zhong, M., Lin, Y., Liu, L.
15-04-2022
PLoS One
https://doi.org/10.1371/journal.pone.0267186

Dengue is a major public health issue worldwide and severe dengue (SD) is life threatening. It is critical to triage patients with dengue infection in the early stage. However, there is limited knowledge on early indicators of SD. The objective of this study is to identify risk factors for the prognosis of SD and try to find out some potential predictive factors for SD from dengue fever (DF) in the early of infection. The PubMed, Cochrane Library and Web of Science databases were searched for relevant studies from June 1999 to December 2020. The pooled odds ratio (OR) or standardized mean difference (SMD) with 95% confidence intervals (CI) of identified factors was calculated using a fixed or random effect model in the meta-analysis. Tests for heterogeneity, publication bias, subgroup analyses, meta-regression, and a sensitivity analysis were further performed. A total of 6,848 candidate articles were retrieved, 87 studies with 35,184 DF and 8,173 SD cases met the eligibility criteria. A total of 64 factors were identified, including population and virus characteristics, clinical symptoms and signs, laboratory biomarkers, cytokines, and chemokines; of these factors, 34 were found to be significantly different between DF and SD, while the other 30 factors were not significantly different between the two groups after pooling the data from the relevant studies. Additionally, 9 factors were positive associated with SD within 7 days after illness when the timing subgroup analysis were performed. Practical factors and biomarkers for the identification of SD were established, which will be helpful for a prompt diagnosis and early effective treatment for those at greatest risk. These outcomes also enhance our knowledge of the clinical manifestations and pathogenesis of SD.

Mosquito survey in Mauritania: Detection of Rift Valley fever virus and dengue virus and the determination of feeding patterns.

Stoek, F., Barry, Y., Ba, A., Schulz, A., Rissmann, M., Wylezich, C., Sadeghi, B., Beyit, A., Eisenbarth, A., N'diaye, F., Haki, M.,

Doumbia, B., Gueya, M., Bah, M., Eiden, M., Groschup, M.
15-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010203

In Mauritania, several mosquito-borne viruses have been reported that can cause devastating diseases in animals and humans. However, monitoring data on their occurrence and local distribution are limited. Rift Valley fever virus (RVFV) is an arthropod-borne virus that causes major outbreaks throughout the African continent and the Arabian Peninsula. The first Rift Valley fever (RVF) epidemic in Mauritania occurred in 1987 and since then the country has been affected by recurrent outbreaks of the disease. To gain information on the occurrence of RVFV as well as other mosquito-borne viruses and their vectors in Mauritania, we collected and examined 4,950 mosquitoes, belonging to four genera and 14 species. The mosquitoes were captured during 2018 in the capital Nouakchott and in southern parts of Mauritania. Evidence of RVFV was found in a mosquito pool of female Anopheles pharoensis mosquitoes collected in December on a farm near the Senegal River. At that time, 37.5% of 16 tested Montbéliarde cattle on the farm showed RVFV-specific IgM antibodies. Additionally, we detected IgM antibodies in 10.7% of 28 indigenous cattle that had been sampled on the same farm one month earlier. To obtain information on potential RVFV reservoir hosts, blood meals captured engorged mosquitoes were analyzed. The mosquitoes mainly fed on humans (urban areas) and cattle (rural areas), but also on small ruminants, donkeys, cats, dogs and straw-colored fruit bats. Results of this study demonstrate the circulation of RVFV in Mauritania and thus the need for further research to investigate the distribution of the virus and its vectors. Furthermore, factors that may contribute to its maintenance should be analyzed more closely. In addition, two mosquito pools containing Aedes aegypti and Culex quinquefasciatus mosquitoes showed evidence of dengue virus (DENV) 2 circulation in the city of Rosso. Further studies are therefore needed to also examine DENV circulation in Mauritania.

Aedes aegypti sialokinin facilitates mosquito blood feeding and modulates host immunity and vascular biology.

Martin-Martin, I., Valenzuela Leon, P., Amo, L., Shrivastava, G., Iniguez, E., Aryan, A., Brooks, S., Kojin, B., Williams, A., Bolland, S., Ackerman, H., Adelman, Z., Calvo, E.
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Cell Rep
https://pubmed.ncbi.nlm.nih.gov/35417706

Saliva from mosquitoes contains vasodilators that antagonize vasoconstrictors produced at the bite site. Sialokinin is a vasodilator present in the saliva of Aedes aegypti. Here, we investigate its function and describe its mechanism of action during blood feeding. Sialokinin induces nitric oxide release similar to substance P. Sialokinin-KO mosquitoes produce lower blood perfusion than parental mosquitoes at the bite site during probing and have significantly longer probing times, which result in lower blood feeding success. In contrast, there is no difference in feeding between KO and parental mosquitoes when using artificial membrane feeders or mice that are treated with a substance P receptor antagonist, confirming that sialokinin interferes with host hemostasis via NK1R signaling. While sialokinin-KO saliva does not affect virus infection in vitro, it stimulates macrophages and inhibits leukocyte recruitment in vivo. This work highlights the biological functionality of salivary proteins in blood feeding.

A Zika virus mutation enhances transmission potential and confers escape from protective dengue virus immunity.

Regla-Nava, J., Wang, Y., Fontes-Garfias, C., Liu, Y., Syed, T., Susantono, M., Gonzalez, A., Viramontes, K., Verma, S., Kim, K., Landeras-Bueno, S., Huang, C., Prigozhin, D., Gleeson, J., Terskikh, A., Shi, P., Shresta, S.
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Cell Rep
https://pubmed.ncbi.nlm.nih.gov/35417697

Zika virus (ZIKV) and dengue virus (DENV) are arthropod-borne pathogenic flaviviruses that co-circulate in many countries. To understand some of the pressures that influence ZIKV evolution, we mimic the natural transmission cycle by repeating serial passaging of ZIKV through cultured mosquito cells and either DENV-naive or DENV-immune mice. Compared with wild-type ZIKV, the strains passaged under both conditions exhibit increased pathogenesis in DENV-immune mice. Application of reverse genetics identifies an isoleucine-to-valine mutation (I39V) in the NS2B proteins of both passaged strains that confers enhanced fitness and escape from pre-existing DENV immunity. Introduction of I39V or I39T, a naturally occurring homologous mutation detected in recent ZIKV isolates, increases the replication of wild-type ZIKV in human neuronal precursor cells and laboratory-raised mosquitoes. Our data indicate that ZIKV strains with enhanced transmissibility and pathogenicity can emerge in DENV-naive or -immune settings, and that NS2B-I39 mutants may represent ZIKV variants of interest.

Sex-specific distribution and classification of Wolbachia infections and mitochondrial DNA haplogroups in Aedes albopictus from the Indo-Pacific.

Yang, Q., Chung, J., Robinson, K., Schmidt, T., Ross, P., Liang, J., Hoffmann, A.
13-04-2022
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https://doi.org/10.1371/journal.pntd.0010139

The arbovirus vector Aedes albopictus (Asian tiger mosquito) is common throughout the Indo-Pacific region, where most global dengue transmission occurs. We analysed population genomic data and tested for cryptic species in 160 Ae. albopictus sampled from 16 locations across this region. We

found no evidence of cryptic Ae. albopictus but found multiple intraspecific COI haplotypes partitioned into groups representing three Asian lineages: East Asia, Southeast Asia and Indonesia. Papua New Guinea (PNG), Vanuatu and Christmas Island shared recent coancestry, and Indonesia and Timor-Leste were likely invaded from East Asia. We used a machine learning trained on morphologically sexed samples to classify sexes using multiple genetic features and then characterized the wAlbA and wAlbB Wolbachia infections in 664 other samples. The wAlbA and wAlbB infections as detected by qPCR showed markedly different patterns in the sexes. For females, most populations had a very high double infection incidence, with 67% being the lowest value (from Timor-Leste). For males, the incidence of double infections ranged from 100% (PNG) to 0% (Vanuatu). Only 6 females were infected solely by the wAlbA infection, while rare uninfected mosquitoes were found in both sexes. The wAlbA and wAlbB densities varied significantly among populations. For mosquitoes from Torres Strait and Vietnam, the wAlbB density was similar in single-infected and superinfected (wAlbA and wAlbB) mosquitoes. There was a positive association between wAlbA and wAlbB infection densities in superinfected Ae. albopictus. Our findings provide no evidence of cryptic species of Ae. albopictus in the region and suggest site-specific factors influencing the incidence of Wolbachia infections and their densities. We also demonstrate the usefulness of ddRAD tag depths as sex-specific mosquito markers. The results provide baseline data for the exploitation of Wolbachia-induced cytoplasmic incompatibility (CI) in dengue control.

Two Conserved Phenylalanine Residues in the E1 Fusion Loop of Alphaviruses Are Essential for Viral Infectivity.

Lucas, C., Davenport, B., Carpentier, K., Tinega, A., Morrison, T.
13-04-2022
J Virol
https://doi.org/10.1128/jvi.00064-22

Alphaviruses infect cells by a low pH-dependent fusion reaction between viral and host cell membranes that is mediated by the viral E1 glycoprotein. Most reported alphavirus E1 sequences include two phenylalanines (F87 and F95) in the fusion loop, yet the role of these residues in viral infectivity remains to be defined. Following introduction of wild type (WT), E1-F87A, and E1-F95A chikungunya virus (CHIKV) RNA genomes into cells, viral particle production was similar in magnitude. However, CHIKV E1-F87A and E1-F95A virions displayed impaired infectivity compared with WT CHIKV particles. Although WT, E1-F87A, and E1-F95A particles bound cells with similar efficiencies, E1-F87A and E1-F95A particles were unable to undergo fusion and entry into cells. Introduction of an F95A mutation in the E1 fusion loop of Mayaro virus or Venezuelan equine encephalitis virus also resulted in poorly infectious virions. We further tested whether an E1-F87A or E1-F95A mutation could be incorporated into a live-attenuated vaccine strain, CHIKV 181/25, to enhance vaccine safety. Infection of immunocompromised *Ifnar1*$^{-/-}$ and *Irf3*$^{-/-}$*Irf5*$^{-/-}$*Irf7*$^{-/-}$ mice with 181/25$^{E1\text{-}F87A}$ or 181/25$^{E1\text{-}F95A}$ resulted in 0% mortality, compared with 100% mortality following 181/25 infection. Despite this enhanced attenuation, surviving *Ifnar1*$^{-/-}$ and *Irf3*$^{-/-}$*Irf5*$^{-/-}$*Irf7*$^{-/-}$ mice were protected against virulent virus re-challenge. Moreover, single-dose immunization of WT mice with either 181/25, 181/25$^{E1\text{-}F87A}$, or 181/25$^{E1\text{-}F95A}$ elicited CHIKV-specific antibody responses and protected against pathogenic CHIKV challenge. These studies define a critical function for residues E1-F87 and E1-F95 in alphavirus fusion and entry into target cells and suggest that incorporation of these mutations could enhance the safety of live-attenuated alphavirus vaccine candidates. IMPORTANCE Alphaviruses are human pathogens that cause both debilitating acute and chronic musculoskeletal disease and potentially fatal encephalitis. In this study, we determined that two highly conserved phenylalanine residues in the alphavirus E1 glycoprotein are required for fusion of viral and host cell membranes and viral entry into target cells. We further demonstrated that mutation of these phenylalanines results in a substantial loss of viral virulence but not immunogenicity. These data enhance an understanding of the viral determinants of alphavirus entry into host cells and could contribute to the development of new antivirals targeting these conserved phenylalanines or new live-attenuated alphavirus vaccines.

First case of Zika virus infection during an outbreak of chikungunya in a rural region of Maharashtra state, India.

Gurav, Y., Alagarasu, K., Yadav, P., Sapkal, G., Gokhale, M., Parashar, D., Jadhav, U., Bote, M., Kakade, M., Nyayanit, D., Kumar, A., Deshpande, G., Cherian, S., Awate, P., Abraham, P.
12-04-2022
Trans R Soc Trop Med Hyg
https://pubmed.ncbi.nlm.nih.gov/35415761

In July 2021, an outbreak of chikungunya virus (CHIKV) was reported in a rural region of Maharashtra state, India. Serum samples of symptomatic cases (n=33) were screened for dengue virus (DENV), CHIKV and Zika virus (ZIKV) by molecular and serological assays. The first case of ZIKV infection from Maharashtra was detected and confirmed by molecular and serological assays. Complete genome sequencing revealed that the ZIKV sequence belongs to the Asian genotype and had a closer homology with pre-epidemic strains present before 2007. ZIKV surveillance needs to be strengthened in the regions experiencing dengue and chikungunya outbreaks.

Cross-tissue and generation predictability of relative Wolbachia densities in the mosquito Aedes aegypti.

Mejia, A., Dutra, H., Jones, M., Perera, R., McGraw, E.
12-04-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05231-9

The insect endosymbiotic bacterium Wolbachia is being deployed in field populations of the mosquito Aedes aegypti for biological control. This microbe prevents the replication of human disease-causing viruses inside the vector, including dengue, Zika and chikungunya. Relative Wolbachia densities may in part predict the strength of this 'viral blocking' effect. Additionally, Wolbachia densities may affect the strength of the reproductive manipulations it induces, including cytoplasmic incompatibility (CI), maternal inheritance rates or induced fitness effects in the insect host. High rates of CI and maternal inheritance and low rates of fitness effects are also key to the successful spreading of Wolbachia through vector populations and its successful use in biocontrol. The factors that control Wolbachia densities are not completely understood. We used quantitative PCR-based methods to estimate relative density of the Wolbachia wAlbB strain in both the somatic and reproductive tissues of adult male and female mosquitoes, as well as in eggs. Using correlation analyses, we assessed whether densities in one tissue predict those in others within the same individual, but also across generations. We found little relationship among the relative Wolbachia densities of different tissues in the same host. The results also show that there was very little relationship between Wolbachia densities in parents and those in offspring, both in the same and different tissues. The one exception was with ovary-egg relationships, where there was a strong positive association. Relative Wolbachia densities in reproductive tissues were always greater than those in the somatic tissues. Additionally, the densities were consistent in females over their lifetime regardless of tissue, whereas they were generally higher and more variable in males, particularly in the testes. Our results indicate that either stochastic processes or local tissue-based physiologies are more likely factors dictating Wolbachia densities in Ae. aegypti individuals, rather than shared embryonic environments or heritable genetic effects of the mosquito genome. These findings have implications for understanding how relative Wolbachia densities may evolve and/or be maintained over the long term in Ae. aegypti.

Zika Virus Induces Mitotic Catastrophe in Human Neural Progenitors by Triggering Unscheduled Mitotic Entry in the Presence of DNA Damage While Functionally Depleting Nuclear PNKP.

Rychlowska, M., Agyapong, A., Weinfeld, M., Schang, L.
12-04-2022
J Virol
https://doi.org/10.1128/jvi.00333-22

Vertical transmission of Zika virus (ZIKV) leads with high frequency to congenital ZIKV syndrome (CZS), whose worst outcome is microcephaly. However, the mechanisms of congenital ZIKV neurodevelopmental pathologies, including direct cytotoxicity to neural progenitor cells (NPC), placental insufficiency, and immune responses, remain incompletely understood. At the cellular level, microcephaly typically results from death or insufficient proliferation of NPC or cortical neurons. NPC replicate fast, requiring efficient DNA damage responses to ensure genome stability. Like congenital ZIKV infection, mutations in the polynucleotide 5'-kinase 3'-phosphatase (PNKP) gene, which encodes a critical DNA damage repair enzyme, result in recessive syndromes often characterized by congenital microcephaly with seizures (MCSZ). We thus tested whether there were any links between ZIKV and PNKP. Here, we show that two PNKP phosphatase inhibitors or PNKP knockout inhibited ZIKV replication. PNKP relocalized from the nucleus to the cytoplasm in infected cells, colocalizing with the marker of ZIKV replication factories (RF) NS1 and resulting in functional nuclear PNKP depletion. Although infected NPC accumulated DNA damage, they failed to activate the DNA damage checkpoint kinases Chk1 and Chk2. ZIKV also induced activation of cytoplasmic CycA/CDK1 complexes, which trigger unscheduled mitotic entry. Inhibition of CDK1 activity inhibited ZIKV replication and the formation of RF, supporting a role of cytoplasmic CycA/CDK1 in RF morphogenesis. In brief, ZIKV infection induces mitotic catastrophe resulting from unscheduled mitotic entry in the presence of DNA damage. PNKP and CycA/CDK1 are thus host factors participating in ZIKV replication in NPC, and pathogenesis to neural progenitor cells. IMPORTANCE The 2015-2017 Zika virus (ZIKV) outbreak in Brazil and subsequent international epidemic revealed the strong association between ZIKV infection and congenital malformations, mostly neurodevelopmental defects up to microcephaly. The scale and global expansion of the epidemic, the new ZIKV outbreaks (Kerala state, India, 2021), and the potential burden of future ones pose a serious ongoing risk. However, the cellular and molecular mechanisms resulting in microcephaly remain incompletely understood. Here, we show that ZIKV infection of neuronal progenitor cells results in cytoplasmic sequestration of an essential DNA repair protein itself associated with microcephaly, with the consequent accumulation of DNA damage, together with an unscheduled activation of cytoplasmic CDK1/Cyclin A complexes in the presence of DNA damage. These alterations result in mitotic catastrophe of neuronal progenitors, which would lead to a depletion of cortical neurons during development.

Single-cell temporal analysis of natural dengue infection reveals skin-homing lymphocyte expansion one day before defervescence.

Arora, J., Opasawatchai, A., Poonpanichakul, T., Jiravejchakul, N., Sungnak, W., DENFREE Thailand, Matangkasombut, O., Teichmann, S., Matangkasombut, P., Charoensawan, V.
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Effective clinical management of acute dengue virus (DENV) infection relies on the timing of suitable treatments during the disease progression. We analyzed single-cell transcriptomic profiles of the peripheral blood mononuclear cell samples from two DENV patients, collected daily during acute phase and also at convalescence. Key immune cell types demonstrated different dynamic responses over the course of

the infection. On the day before defervescence (Day -1), we observed the peak expression of several prominent genes in the adaptive immunological pathways. We also characterized unique effector T cell clusters that expressed skin-homing signature genes at Day -1, whereas upregulation of skin and gut homing genes was also observed in plasma cells and plasmablasts during the febrile period. This work provides an overview of unique molecular dynamics that signify the entry of the critical phase, and the findings could improve the patient management of DENV infection.

Design, synthesis, and biological evaluation of novel 2'-methyl-2'-fluoro-6-methyl-7-alkynyl-7-deazapurine nucleoside analogs as anti-Zika virus agents.

Yao, G., Yu, J., Lin, C., Zhu, Y., Duan, A., Li, M., Yuan, J., Zhang, J.
11-03-2022
Eur J Med Chem
https://pubmed.ncbi.nlm.nih.gov/35306290

Zika virus (ZIKV) is a mosquito-borne flavivirus and outbreaks of ZIKV have been reported in Africa, Americas and other parts of the world lately. The ZIKV epidemic has received extensive attention due to its ability to cause serious medical consequences and complications such as microcephaly and Guillain-Barre syndrome in recent years. Up to now, there are no specific treatments or vaccines available for ZIKV infection, which highlights the urgent need for developing new therapies. In this work, we designed and synthesized a series of novel 6-methyl-7-acetylenenyl-7-deazapurine nucleoside analogs as potential inhibitors of ZIKV replication. The biological activities against ZIKV replication were evaluated and the structure-activity relationship (SAR) was also studied. Among the compounds evaluated, nucleoside analog 38 (EC_{50} = 2.8 ± 0.8 μM, EC_{90} = 6.8 ± 2.3 μM) showed the most potent anti-ZIKV activity with low cytotoxicity (CC_{50} = 54.1 ± 6.9 μM) in an A549 based cellular model. The inhibitory activity of 38 was about 5 times more potent than the positive control NITD008. Notably, 38 showed similar inhibition potency against different ZIKV strains (ZG-01 and MR766) in a variety of host cell types including SNB19, A549, Huh7, Vero. In addition, 38 (K_d = 1.87 μM) has a stronger affinity to ZIKV RNA-dependent RNA polymerase (RdRp) protein than NITD008 (K_d = 3.43 μM) in the non-phosphorylation assay. These results indicated that compound 38 may serve as a promising candidate in future anti-ZIKV drug discovery.

RACK1 Associates with RNA-Binding Proteins Vigilin and SERBP1 to Facilitate Dengue Virus Replication.

Brugier, A., Hafirrassou, M., Pourcelot, M., Baldaccini, M., Kril, V., Couture, L., Kümmerer, B., Gallois-Montbrun, S., Bonnet-Madin, L., Vidalain, P., Delaugerre, C., Pfeffer, S., Meertens, L., Amara, A.
10-03-2022
J Virol
https://doi.org/10.1128/jvi.01962-21

Dengue virus (DENV) is a mosquito-borne flavivirus responsible for dengue disease, a major human health concern for which no effective treatment is available. DENV relies heavily on the host cellular machinery for productive infection. Here, we show that the scaffold protein RACK1, which is part of the DENV replication complex, mediates infection by binding to the 40S ribosomal subunit. Mass spectrometry analysis of RACK1 partners coupled to an RNA interference screen-identified Vigilin and SERBP1 as DENV host-dependency factors. Both are RNA-binding proteins that interact with the DENV genome. Genetic ablation of Vigilin or SERBP1 rendered cells poorly susceptible to DENV, as well as related flaviviruses, by hampering the translation and replication steps. Finally, we established that a Vigilin or SERBP1 mutant lacking RACK1 binding but still interacting with the viral RNA is unable to mediate DENV infection. We propose that RACK1 recruits Vigilin and SERBP1, linking the DENV genome to the translation machinery for efficient infection. IMPORTANCE We recently identified the scaffolding RACK1 protein as an important host-dependency factor for dengue virus (DENV), a positive-stranded RNA virus responsible for the most prevalent mosquito-borne viral disease worldwide. Here, we have performed the first RACK1 interactome in human cells and identified Vigilin and SERBP1 as DENV host-dependency factors. Both are RNA-binding proteins that interact with the DENV RNA to regulate viral replication. Importantly, Vigilin and SERBP1 interact with RACK1 and the DENV viral RNA (vRNA) to mediate viral replication. Overall, our results suggest that RACK1 acts as a binding platform at the surface of the 40S ribosomal subunit to recruit Vigilin and SERBP1, which may therefore function as linkers between the viral RNA and the translation machinery to facilitate infection.

Targeted inhibition of Zika virus infection in human cells by CRISPR-Cas13b.

Chen, P., Chen, M., Chen, Y., Jing, X., Zhang, N., Zhou, X., Li, X., Long, G., Hao, P.
09-02-2022
Virus Res
https://pubmed.ncbi.nlm.nih.gov/35150770

Zika virus (ZIKV) outbreaks occurred in recent years on an unprecedented scale, which caused fever and severe complications like Guillain-Barré syndrome in adults and fetal abnormalities. No vaccines or other effective treatments against ZIKV are available to date. The CRISPR-Cas13 family has the unique ability to target single-strand RNA molecules and mediate RNA cleavage. In the present study, we sought to exploit CRISPR-Cas13b for developing an anti-ZIKV system in mammalian cells. We first generated a ZIKV infection and reporting system by: (1) fusing mCherry to the ZIKV capsid protein for reporting infection by fluorescence; and (2) deriving a 293T cell line (293T-DC-SIGN) stably expressing DC-SIGN (Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin) that became highly susceptible to ZIKV

infection. The CRISPR Cas13b expression was reported to be in the cytoplasm of 293T-DC-SIGN cells using a Cas13b-GFP fusion expression vector. Fourteen CRISPR RNAs (crRNAs) were designed to target the most conserved regions of the ZIKV genome through bioinformatics analysis of 1138 ZIKV genome sequences. Five crRNAs were found to have significant effects ($p < 0.001$; two-sided t test) for Cas13b-targeted inhibition on ZIKV infection in 293T-DC-SIGN cells. Our study demonstrated an exciting example of using the CRISPR-Cas13b system for the treatment and prevention of ZIKV infection, highlighting CRISPR-Cas13 as a promising therapeutic anti-RNA virus strategy.

Gospel of malignant Glioma: Oncolytic virus therapy.

Revue de littérature

Li, J., Meng, Q., Zhou, X., Zhao, H., Wang, K., Niu, H., Wang, Y.
28-01-2022
Gene
https://pubmed.ncbi.nlm.nih.gov/35093451

Glioma accounts for nearly 80% of all intracranial malignant tumors. It is a major challenge to society as it is causes to impaired brain function in many patients. Currently, gliomas are mainly treated with surgery, postoperative radiotherapy, and chemotherapy. However, the curative effects of these treatments are not satisfactory. Oncolytic virus (OV) is a novel treatment which works by activating the immune functions and inducing apoptosis of tumor cells. The OV propagates indefinitely in the host cell, eventually leading to the death of host cell. Subsequently, a large number of antigens and signal molecules are released which exert antitumor immunity. Several preclinical and clinical studies have shown that G207, DNX2401, Zika and other viruses have important roles in malignant tumors. For example, these viruses can reduce the growth of tumor cells without causing severe complications. However, the known OVs have not been clearly classified. Herein, we divided OVs into neurotropic and non-neurophilic OVs based on whether the OVs are naturally neurotropic or not. The therapeutic effects of each group were compared. Finally, challenges encountered in the clinical application of OVs in the treatment of malignant gliomas were summarized.

Differential Impedance Sensing platform for high selectivity antibody detection down to few counts: A case study on Dengue Virus.

Piedimonte, P., Sola, L., Cretich, M., Gori, A., Chiari, M., Marchisio, E., Borga, P., Bertacco, R., Melloni, A., Ferrari, G., Sampietro, M.
15-01-2022
Biosens Bioelectron
https://pubmed.ncbi.nlm.nih.gov/35091373

We developed a biosensing system for serological detection of viruses based on the impedance variation between gold microelectrodes upon the capture of the target antibodies hybridized with nanobeads for signal amplification. The microfluidic platform core features a Differential Impedance Sensing (DIS) architecture between a reference and an active sensor able to reach nanoparticle resolution of few tens. The biosensor, functionalized with a copoly layer housing a synthetic peptide probe, has shown a limit of detection (LOD) below 100 pg/mL using a model IgG antibody spiked in a buffer. The biosensor was also tested with human serum samples for quantitative counts of anti-Dengue Virus antibodies, reaching a sensitivity that outperforms commercial ELISA kit. The system is perfectly suited to be easily reconfigured for novel probes by simply modifying the preparation of the biosensor chip surface, thus addressing a wide range of pathogens and diseases with clinically relevant concentrations for rapid immunoassays in a point of care setting.

Carbon dots and Methylene blue facilitated photometric quantification of Hemoglobin.

Singh, S., Srinivasan, A., Mitra, S., Gooh Pattader, P.
18-01-2022
Spectrochim Acta A Mol Biomol Spectrosc
https://pubmed.ncbi.nlm.nih.gov/35077978

Early detection and monitoring of any abnormality of Hemoglobin (Hb) concentration in whole blood samples are important as this may be related to anemia, leukemia, dengue, etc. To facilitate quantitative detection and to monitor the hemoglobin level in the blood, we attempt to develop a low-cost, portable point of care (POC) device based on the spectrophotometric principle. Optical sensitivities of carbon quantum dots (CDs) are found to be highly responsive, while there is a selective reaction between Hb and reduced form of Methylene Blue (MB_{red}). The interaction of Hb, MB_{red}, and CDs is delineated using UV-Visible (UV-Vis) spectroscopy. CDs have a characteristic UV-Vis peak at ~347 nm, and it shows a gradual increase in intensity with a slight red shift (~355 nm) on the progressive increase in Hb concentration. Simultaneously, the colorless MB_{red} is oxidized to its blue oxidized form MB_{ox} and its characteristic peak starts reappearing at ~663 nm. These responses are exploited to quantify Hb concentration with a limit of detection (LOD) as low as ~2 g dL^{-1} in a developed POC device, and the results are validated with the clinical data obtained from a local hospital with reasonably good agreement. This photometric detection approach can be adopted for other quantitative biosensors.

Evaluation of treatment effect modification by biomarkers measured pre- and post-randomization in the presence of non-monotone missingness.

Zhuang, Y., Huang, Y., Gilbert, P.
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Biostatistics
https://doi.org/10.1093/biostatistics/kxaa040

In vaccine studies, an important research question is to study effect modification of clinical treatment efficacy by

intermediate biomarker-based principal strata. In settings where participants entering a trial may have prior exposure and therefore variable baseline biomarker values, clinical treatment efficacy may further depend jointly on a biomarker measured at baseline and measured at a fixed time after vaccination. This makes it important to conduct a bivariate effect modification analysis by both the intermediate biomarker-based principal strata and the baseline biomarker values. Existing research allows this assessment if the sampling of baseline and intermediate biomarkers follows a monotone pattern, i.e., if participants who have the biomarker measured post-randomization would also have the biomarker measured at baseline. However, additional complications in study design could happen in practice. For example, in a dengue correlates study, baseline biomarker values were only available from a fraction of participants who have biomarkers measured post-randomization. How to conduct the bivariate effect modification analysis in these studies remains an open research question. In this article, we propose approaches for bivariate effect modification analysis in the complicated sampling design based on an estimated likelihood framework. We demonstrate advantages of the proposed method over existing methods through numerical studies and illustrate our method with data sets from two phase 3 dengue vaccine efficacy trials.

RAGE

Distinctive Gross Presentation in Free-ranging White-tailed Deer (Odocoileus virginianus) with Rabies.

Weyna, A., Ruder, M., Dalton, M., Bahnson, C., Keel, M., Fenton, H., Ballard, J., Nemeth, N.
18-04-2022
J Wildl Dis
https://doi.org/10.7589/JWD-D-21-00176

The white-tailed deer (Odocoileus virginianus) is a popular game species in North America and often lives in close proximity to humans and domestic animals. Deer with neurologic signs are of high interest to the general public and wildlife managers because of disease and safety concerns. Our aim was to describe diagnostic findings from free-ranging white-tailed deer diagnosed with rabies from across the eastern US from 2000 to 2021, with emphasis on gross lesions in the skin and soft tissue overlying the skull. We reviewed diagnostic reports of white-tailed deer cases submitted to the Southeastern Cooperative Wildlife Disease Study for those diagnosed with rabies from 2000 to 2021. Rabies virus infection was confirmed by immunohistochemistry or fluorescent antibody test of brain, or both. Nine adult deer from five states were diagnosed with rabies, including seven (78%) females and two (22%) males. Three (33%) deer were found dead, and six (67%) were humanely dispatched for abnormal behavior. Six deer heads were examined grossly and had lesions, including forehead or periorbital alopecia, cutaneous erythema, abrasions and ulcers, and subcutaneous edema. Histologic examination was performed for eight of nine cases, all of which had intraneuronal eosinophilic inclusion (Negri) bodies in cerebrum, cerebellum, or both. Most (6/8; 75%) had perivascular lymphoplasmacytic encephalitis. Rabies should be considered a differential diagnosis in deer with this pattern of head lesions, suggestive of head rubbing or head pressing.

Translocation of an Anteater (Tamandua tetradactyla) Infected with Rabies from Virginia to Tennessee Resulting in Multiple Human Exposures, 2021.

Grome, H., Yackley, J., Goonewardene, D., Cushing, A., Souza, M., Carlson, A., Craig, L., Cranmore, B., Wallace, R., Orciari, L., Niezgoda, M., Panayampalli, S., Gigante, C., Fill, M., Jones, T., Schaffner, W., Dunn, J.
15-04-2022
MMWR Morb Mortal Wkly Rep
https://doi.org/10.15585/mmwr.mm7115a1

On August 16, 2021, the Tennessee Department of Health (TDH) was notified of a positive rabies test result from a South American collared anteater (Tamandua tetradactyla) in Washington County, Tennessee. Tamanduas, or lesser anteaters, are a species of anteater in which rabies has not previously been reported. The animal was living at a Tennessee zoo and had been recently translocated from a zoo in Virginia. TDH conducted an investigation to confirm the rabies result, characterize the rabies variant, and ascertain an exposure risk assessment among persons who came into contact with the tamandua. Risk assessments for 22 persons were completed to determine the need for rabies postexposure prophylaxis (rPEP); rPEP was recommended for 13 persons, all of whom agreed to receive it. Using phylogenetic results of the virus isolated from the tamandua and knowledge of rabies epidemiology, public health officials determined that the animal was likely exposed to wild raccoons present at the Virginia zoo. This report describes expansion of the wide mammalian species diversity susceptible to rabies virus infection and summarizes the investigation, highlighting coordination among veterinary and human public health partners and the importance of preexposure rabies vaccination for animal handlers and exotic zoo animals.

Glu_{333} in rabies virus glycoprotein is involved in virus attenuation through astrocyte infection and interferon responses.

Itakura, Y., Tabata, K., Morimoto, K., Ito, N., Chambaro, H., Eguchi, R., Otsuguro, K., Hall, W., Orba, Y., Sawa, H., Sasaki, M.
22-03-2022
iScience
https://doi.org/10.1016/j.isci.2022.104122

The amino acid residue at position 333 of the rabies virus (RABV) glycoprotein (G333) is a major determinant of RABV pathogenicity. Virulent RABV strains possess Arg_{333}, whereas the attenuated strain HEP-Flury (HEP) possesses Glu_{333}. To investigate the potential attenuation mechanism dependent on a single amino acid at G333, comparative analysis was performed between HEP and $HEP^{333}R$ mutant with Arg_{333}. We examined their respective tropism for astrocytes and the subsequent immune responses in astrocytes. Virus replication and subsequent interferon (IFN) responses in astrocytes infected with HEP were increased compared with $HEP^{333}R$ both *in vitro* and *in vivo*. Furthermore, involvement of IFN in the avirulency of HEP was demonstrated in IFN-receptor knockout mice. These results indicate that Glu_{333} contributes to RABV attenuation by determining the ability of the virus to infect astrocytes and stimulate subsequent IFN responses.

Clofazimine derivatives as potent broad-spectrum antiviral agents with dual-target mechanism.

Zhang, X., Shi, Y., Guo, Z., Zhao, X., Wu, J., Cao, S., Liu, Y., Li, Y., Huang, W., Wang, Y., Liu, Q., Li, Y., Song, D.
05-03-2022
Eur J Med Chem
https://pubmed.ncbi.nlm.nih.gov/35279610

Thirty-two clofazimine derivatives, of which twenty-two were new, were synthesized and evaluated for their antiviral effects against both rabies virus and pseudo-typed SARS-CoV-2, taking clofazimine (1) as the lead. Among them, compound 15f bearing 4-methoxy-2-pyridyl at the N5-position showed superior or comparable antiviral activities to lead 1, with the EC_{50} values of 1.45 μM and 14.6 μM and the SI values of 223 and 6.1, respectively. Compound 15f inhibited rabies and SARS-CoV-2 by targeting G or S protein to block membrane fusion, as well as binding to L protein or nsp13 to inhibit intracellular biosynthesis respectively, and thus synergistically exerted a broad-spectrum antiviral effect. The results provided useful scientific data for the development of clofazimine derivatives into a new class of broad-spectrum antiviral candidates.

TRACHOME

ULCERE DE BURULI

PIAN

LÈPRE

Antimicrobial Resistance among Leprosy Patients in Brazil: Real-World Data Based on the National Surveillance Plan.

Andrade, E., Brandão, J., Silva, J., Coriolano, C., Rosa, P., Moraes, M., Ferreira, C., Gomes, C., Araújo, W.
18-04-2022
Antimicrob Agents Chemother
https://doi.org/10.1128/aac.02170-21

Brazil ranks second among countries for new cases and first for relapse cases of leprosy worldwide. The Mycobacterium leprae Resistance Surveillance Plan was established. We aimed to present the results of a 2-year follow-up of the National Surveillance Plan in Brazil. A cross-sectional study of leprosy cases was performed to investigate antimicrobial resistance (AMR) in Brazil from October 2018 to September 2020. Molecular screening targeting genes related to dapsone (*folP1*), rifampin (*rpoB*), and ofloxacin resistance (*gyrA*) was performed. During the referral period, 63,520 active leprosy patients were registered in Brazil, and 1,183 fulfilled the inclusion criteria for molecular AMR investigation. In total, only 16 (1.4%) patients had genetic polymorphisms associated with AMR. Of these, 8 (50%) had cases of leprosy relapse, 7 (43.8%) had cases of suspected therapeutic failure with standard treatment, and 1 (6.2%) was a case of new leprosy presentation. M. leprae strains with AMR-associated mutations were found for all three genes screened. Isolates from two patients showed simultaneous resistance to dapsone and rifampin, indicating multidrug resistance (MDR). No significant relationship between clinical variables and the presence of AMR was identified. Our study revealed a low frequency of AMR in Brazil. Isolates were resistant mainly to dapsone, and a very low number of isolates were resistant to rifampin, the main bactericidal agent for leprosy, or presented MDR, reinforcing the importance of the standard World Health Organization multidrug therapy. The greater frequency of AMR among relapsed patients supports the need to constantly monitor this group.

An Overview of Treatment Guidelines and Methods of Synthesis of Drugs Used in Leprosy Chemotherapy.

Pinheiro, L., Borges, J., Campos, V., Dantas, L.
15-04-2022
Mini Rev Med Chem
https://doi.org/10.2174/1389557522666220415233627

Leprosy is a neglected tropical disease (NTDs) caused by Mycobacterium leprae (M. leprae). The treatment is considered effective, however, the high dose multidrug therapy (MDT) for a long period and its adverse effects result in the abandonment of the treatment by patients. Indeed, antimicrobial resistance is still an obstacle that must be overcome in the treatment of leprosy. In the present article, we reviewed the WHO guidelines for the chemotherapy of

leprosy and the methods of synthesis of these drugs.

Leprosy in Mayotte: persistent hyper-endemicity in a French overseas territory.

Maillard, O., Tabard, C., Mohand-Oussaid, D., Cazal, Y., Saidy, H., de Montera, A., Bourée, P., Bertolotti, A.
16-04-2022
J Eur Acad Dermatol Venereol
https://doi.org/10.1111/jdv.18160

LRRK2 as a target for modulating immune system responses.

Russo, I., Bubacco, L., Greggio, E.
12-04-2022
Neurobiol Dis
https://pubmed.ncbi.nlm.nih.gov/35427743

Mutations in the Leucine-Rich Repeat Kinase 2 (LRRK2) gene are associated with familial and sporadic cases of Parkinson's disease (PD) but are also found in patients with immune-related disorders, such as inflammatory bowel disease (IBD) and leprosy, linking LRRK2 to the immune system. Supporting this genetic evidence, in the last decade LRRK2 was robustly shown to modulate inflammatory responses at both systemic and central nervous system level. In this review, we recapitulate the role of LRRK2 in central and peripheral inflammation in PD and inflammatory disease models. Moreover, we discuss how LRRK2 inhibitors and anti-inflammatory drugs may be beneficial at reducing disease risk/progression in LRRK2-mutation carriers and manifesting PD patients, thus supporting LRRK2 as a promising disease-modifying PD strategy.

Theoretical frameworks for project goal-setting: A qualitative case study of an organisational practice in Nigeria.

Ogbeiwi, O.
14-04-2022
Int J Health Plann Manage
https://doi.org/10.1002/hpm.3471

Goal-setting in any practice context is vague unless the process is based on a framework that produces good goals. Popular goal-setting frameworks construct Specific, Measurable, Attainable, Realistic, and Time-bound (SMART) goal statements. Yet, research of how healthcare goals that are foundational to health plans are formulated is scanty. This case study explored the goal-setting practice of an organisation in Nigeria to discover the theoretical frameworks for setting the goals of their leprosy projects. The study triangulated individual semi-structured interviews of 10 leprosy managers with a review of their project plans and a participant observation of the organisation's annual planning event. A five-stage thematic analysis was used to serially identify, code, and integrate goal-setting themes from the data collected. This produced three final emergent themes: stakeholders, strategy, and goal statements, with 11 associated conceptual frameworks. All were further theoretically integrated into one general framework that illustrates the organisational goal-setting practice at the time of study. This revealed a practice with a four-staged linear centre-driven process that led to a top-down, problem-based goal formulation, and produced assigned project plans based on hierarchical non-SMART goal statements. Collaborative goal-setting process is proposed for Specific, Measurable, Attainable, Realistic, Timed, and Agreeable statements of project objectives and aims written with Change, Beneficiaries, Indicator, Target, Timeframe and Change, Beneficiaries, Location, and Timeframe models respectively.

The end of leprosy is not imminent, but it is on the horizon.

Saunderson, P., Duck, M.
14-04-2022
Indian J Med Res
https://doi.org/10.4103/ijmr.ijmr_3654_21

Population-wide active case finding and prevention for tuberculosis and leprosy elimination in Kiribati: the PEARL study protocol.

Coleman, M., Hill, J., Timeon, E., Tonganibeia, A., Eromanga, B., Islam, T., Trauer, J., Chambers, S., Christensen, A., Fox, G., Marks, G., Britton, W., Marais, B.
12-04-2022
BMJ Open
https://doi.org/10.1136/bmjopen-2021-055295

Population-wide interventions offer a pathway to tuberculosis (TB) and leprosy elimination, but 'real-world' implementation in a high-burden setting using a combined approach has not been demonstrated. This implementation study aims to demonstrate the feasibility and evaluate the effect of population-wide screening, treatment and prevention on TB and leprosy incidence rates, as well as TB transmission. A non-randomised 'screen-and-treat' intervention conducted in the Pacific atoll of South Tarawa, Kiribati. Households are enumerated and all residents ≥3 years, as well as children <3 years with recent household exposure to TB or leprosy, invited for screening. Participants are screened using tuberculin skin testing, signs and symptoms of TB or leprosy, digital chest X-ray with computer-aided detection and sputum testing (Xpert MTB/RIF Ultra). Those diagnosed with disease are referred to the National TB and Leprosy Programme for management. Participants with TB infection are offered TB preventive treatment and those without TB disease or infection, or leprosy, are offered leprosy prophylaxis. The primary study outcome is the difference in the annual TB case notification rate before and after the intervention; a similar outcome is included for leprosy. The effect on TB transmission will be measured by comparing the estimated annual risk of TB infection in primary school children before and after the intervention, as a co-primary outcome used for power calculations. Comparison of TB and leprosy case notification

rates in South Tarawa (the intervention group) and the rest of Kiribati (the control group) before, during and after the intervention is a secondary outcome. Approval was obtained from the University of Sydney Human Research Ethics Committee (project no. 2021/127) and the Kiribati Ministry of Health and Medical Services (MHMS). Findings will be shared with the MHMS and local communities, published in peer-reviewed journals and presented at international conferences.

Leprosy: A Life-Changing Disease.

Zhang, Y., Feng, L., Wang, L.
12-04-2022
J Eur Acad Dermatol Venereol
https://doi.org/10.1111/jdv.18144

TRYPANOSOMES (TRYPANOSOMIASE ET MALADIE DE CHAGAS)

The influence of abiotic and biotic variables on the patent parasitemias of Trypanosoma spp. in Thrichomys fosteri (Rodentia: Echimyidae) in the southern Pantanal.

Santos, F., Sano, N., Liberal, S., Nantes, W., Sanabria, I., Dos Santos, G., Martinelli, A., de Oliveira, C., Almeida-Gomes, M., Jansen, A., Herrera, H.
18-04-2022
Parasitol Res
https://doi.org/10.1007/s00436-022-07522-7

Parasitism is a dynamic ecological phenomenon that is constantly influenced by the environment and intrinsic factors of the host. We aimed to evaluate the influence of vegetation, environmental temperature, reproductive conditions, sex, and body condition (BC) on the detection of Trypanosoma spp. in the blood of Thrichomys fosteri in the Pantanal region, an enzootic area for trypanosomiasis. Whole blood was collected from the tip of the tail, and nPCR was performed for Trypanosoma spp. detection from the DNA extracted from the resultant blood clot. Statistical analyses were performed using generalized linear models. Our results showed that there is a greater probability of detection of Trypanosoma spp. in the bloodstream of animals with the highest BC values in periods with mild temperatures. Since T. fosteri is an abundant and common prey for carnivores, even in periods with low temperatures and consequent decrease in the reproduction and activities of the blood-sucking arthropod vectors, the maintenance of Trypanosoma spp. in the studied area would be guaranteed via predation (trophic network) of T. fosteri individuals with good BC and patent parasitemia. Furthermore, T. fosteri, which displays Trypanosoma spp. in the bloodstream, would be reproducing adequately because we found no influence between the reproductive condition and the detection of Trypanosoma spp. in T. fosteri. The caviomorph rodent T. fostei is an important species for the maintenance of Trypanosoma spp. in the Pantanal biome.

Two-year death prediction models among patients with Chagas Disease using machine learning-based methods.

Ferreira, A., Santos, L., Sabino, E., Ribeiro, A., Oliveira-da Silva, L., Damasceno, R., D'Angelo, M., Nunes, M., Haikal, D.
14-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010356

Chagas disease (CD) is recognized by the World Health Organization as one of the thirteen most neglected tropical diseases. More than 80% of people affected by CD will not have access to diagnosis and continued treatment, which partly supports the high morbidity and mortality rate. Machine Learning (ML) can identify patterns in data that can be used to increase our understanding of a specific problem or make predictions about the future. Thus, the aim of this study was to evaluate different models of ML to predict death in two years of patients with CD. ML models were developed using different techniques and configurations. The techniques used were: Random Forests, Adaptive Boosting, Decision Tree, Support Vector Machine, and Artificial Neural Networks. The adopted settings considered only interview variables, only complementary exam variables, and finally, both mixed. Data from a cohort study with CD patients called SaMi-Trop were analyzed. The predictor variables came from the baseline; and the outcome, which was death, came from the first follow-up. All models were evaluated in terms of Sensitivity, Specificity and G-mean. Among the 1694 individuals with CD considered, 134 (7.9%) died within two years of follow-up. Using only the predictor variables from the interview, the different techniques achieved a maximum G-mean of 0.64 in predicting death. Using only the variables from complementary exams, the G-mean was up to 0.77. In this configuration, the protagonism of NT-proBNP was evident, where it was possible to observe that an ML model using only this single variable reached G-mean of 0.76. The configuration that mixed interview variables and complementary exams achieved G-mean of 0.75. ML can be used as a useful tool with the potential to contribute to the management of patients with CD, by identifying patients with the highest probability of death. Trial Registration: This trial is registered with ClinicalTrials.gov, Trial ID: NCT02646943.

Heterologous production of ascofuranone and ilicicolin A in Aspergillus sojae.

Araki, Y., Shinohara, Y., Hara, S., Sato, A., Sakaue, R., Gomi, K., Kita, K., Ito, K.
13-04-2022
J Gen Appl Microbiol
https://doi.org/10.2323/jgam.2021.08.001

Ascofuranone and its precursor, ilicicolin A, are secondary metabolites with various pharmacological activities that are

produced by Acremonium egyptiacum. In particular, ascofuranone strongly inhibits trypanosome alternative oxidase and represents a potential drug candidate against African trypanosomiasis. However, difficulties associated with industrial production of ascofuranone by A. egyptiacum, specifically the co-production of ascochlorin, which inhibits mammalian respiratory chain complex III at low concentrations, has precluded its widespread application. Therefore, in this study, ascofuranone biosynthetic genes (ascA-E and H-J) were heterologously expressed in Aspergillus sojae, which produced very low-levels of endogenous secondary metabolites under conventional culture conditions. As a result, although we obtained transformants producing both ilicicolin A and ascofuranone, they were produced only when an adequate concentration of chloride ions was added to the medium. In addition, we succeeded in increasing the production of ilicicolin A, by enhancing the expression of the rate-determining enzyme AscD, using a multi-copy integration system. The heterologous expression approach described here afforded the production of both ascofuranone and ilicicolin A, allowing for their development as therapeutics.

Effectiveness of Nifurtimox in the Treatment of Chagas Disease: a Long-Term Retrospective Cohort Study in Children and Adults.

Falk, N., Berenstein, A., Moscatelli, G., Moroni, S., González, N., Ballering, G., Freilij, H., Altcheh, J.
13-04-2022
Antimicrob Agents Chemother
https://doi.org/10.1128/aac.02021-21

Chagas disease (ChD), caused by Trypanosoma cruzi, has a global prevalence due to patient migration. However, despite its worldwide distribution, long-term follow-up efficacy studies with nifurtimox (NF) are scarce and have been conducted with only small numbers of patients. A retrospective study of a large cohort of ChD treated children and adults with NF. Treatment response was evaluated by clinical, parasitological, and serological after-treatment evaluation. A total of 289 patients were enrolled, of which 199 were children and 90 adults. At diagnosis, 89.6% of patients were asymptomatic. Overall, all symptomatic patients showed clinical improvement. At baseline, parasitemia was positive in 130 of 260 (50%) patients. All but one adult patient had cleared their parasitemia by the end of treatment. That patient was considered a treatment failure. Median follow-up time for children was 37.7 months, with an interquartile range of (IQR_{25-75} 12.2 to 85.3), and for adults was 14.2 months (IQR_{25-75}, 1.9 to 33.8). After treatment, a decrease of T. cruzi antibodies and seroconversion were observed in 34.6% of patients. The seroconversion profile showed that, the younger the patient, the higher the rate of seroconversion (log rank test; *P* value, <0.01). At least 20% seroreduction at 1 year follow-up was observed in 33.2% of patients. Nifurtimox was highly effective for ChD treatment. Patients had excellent treatment responses with fully resolved symptoms related to acute T. cruzi infection. Clearance of parasitemia and a decrease in T. cruzi antibodies were observed as markers of treatment response. This study reinforces the importance of treating patients during childhood since the treatment response was more marked in younger subjects. (This protocol was registered at ClinicalTrials.gov under registration number NCT04274101).

Transmigration of *Trypanosoma brucei* across an *in vitro* blood-cerebrospinal fluid barrier.

Speidel, A., Theile, M., Pfeiffer, L., Herrmann, A., Figarella, K., Ishikawa, H., Schwerk, C., Schroten, H., Duszenko, M., Mogk, S.
01-03-2022
iScience
https://doi.org/10.1016/j.isci.2022.104014

Trypanosoma brucei is the causative agent of human African trypanosomiasis. The parasite transmigrates from blood vessels across the choroid plexus epithelium to enter the central nervous system, a process that leads to the manifestation of second stage sleeping sickness. Using an *in vitro* model of the blood-cerebrospinal fluid barrier, we investigated the mechanism of the transmigration process. For this, a monolayer of human choroid plexus papilloma cells was cultivated on a permeable membrane that mimics the basal lamina underlying the choroid plexus epithelial cells. Plexus cells polarize and interconnect forming tight junctions. Deploying different *T. brucei brucei* strains, we observed that geometry and motility are important for tissue invasion. Using fluorescent microscopy, the parasite's moving was visualized between plexus epithelial cells. The presented model provides a simple tool to screen trypanosome libraries for their ability to infect cerebrospinal fluid or to test the impact of chemical substances on transmigration.

LEISHMANIOSE

Leishmania LiHyC protein is immunogenic and induces protection against visceral leishmaniasis.

Machado, A., Lage, D., Vale, D., Freitas, C., Linhares, F., Cardoso, J., Oliveira-da-Silva, J., Pereira, I., Ramos, F., Tavares, G., Ludolf, F., Bandeira, R., Maia, L., Menezes-Souza, D., Duarte, M., Chávez-Fumagalli, M., Roatt, B., Christodoulides, M., Martins, V., Coelho, E.
18-04-2022
Parasite Immunol
https://doi.org/10.1111/pim.12921

Treatment against visceral leishmaniasis (VL) presents problems by toxicity of drugs, high cost and/or emergence of resistant strains. The diagnosis is hampered by variable sensitivity and/or specificity of tests. In this context, prophylactic vaccination could represent a control measure against disease. In this study, the protective efficacy from Leishmania LiHyC protein was evaluated in murine model against Leishmania infantum infection. LiHyC was used as

recombinant protein (rLiHyC) associated with saponin (rLiHyC/S) or Poloxamer 407-based polymeric micelles (rLiHyC/M) to immunize mice. Animals received also saline, saponin or empty micelles as controls. The immunogenicity was evaluated before and after challenge, and results showed that vaccination with rLiHyC/S or rLiHyC/M induced the production of high levels of IFN-γ, IL-12 and GM-CSF in cell culture supernatants, as well as higher IFN-γ expression evaluated by RT-qPCR and involvement from $CD4^+$ and $CD8^+$ T cell subtypes producing IFN-γ, TNF-α and IL-2. A positive lymphoproliferative response was also found in cell cultures from vaccinated animals, besides high levels of rLiHyC- and parasite-specific nitrite and IgG2a antibodies. Immunological assays correlated with significant reductions in the parasite load in spleens, livers, bone marrows and draining lymph nodes from vaccinated mice, when compared to values found in the controls. The micellar composition showed slightly better immunological and parasitological data, as compared to rLiHyC/S. Results suggest that rLiHyC associated with adjuvants could be considered for future studies as a vaccine candidate against VL.

Zinc in dermatology.

Revue de littérature

Searle, T., Ali, F., Al-Niaimi, F.
18-04-2022
J Dermatolog Treat
https://doi.org/10.1080/09546634.2022.2062282

Zinc has numerous pharmacological uses in dermatology. Its antioxidant and immunomodulatory properties are thought to correlate with its efficacy in acne vulgaris and leishmaniasis, amongst other cutaneous conditions. We conducted a review of the literature on the use of zinc in dermatology; in particular, we investigated its role in acne vulgaris, hair loss, hidradenitis suppurativa, leishmaniasis, and warts. We searched MEDLINE selecting only articles in English and evaluating the evidence using the Oxford Center of Evidence-Based Medicine 2011 guidance. This review has found evidence to support the use of zinc in patients in infectious conditions (leishmaniasis and warts), inflammatory conditions (acne rosacea, hidradenitis suppurativa) and in hair loss disorders.Ppatients with zinc deficiency should also receive oral supplementation. Further research and large randomized controlled trials are required to investigate the role of zinc as a monotherapy.

Transcriptional profiling of macrophages reveals distinct parasite stage-driven signatures during early infection by Leishmania donovani.

Chaparro, V., Graber, T., Alain, T., Jaramillo, M.
16-04-2022
Sci Rep
https://doi.org/10.1038/s41598-022-10317-6

Macrophages undergo swift changes in mRNA abundance upon pathogen invasion. Herein we describe early remodelling of the macrophage transcriptome during infection by amastigotes or promastigotes of Leishmania donovani. Approximately 10-16% of host mRNAs were differentially modulated in L. donovani-infected macrophages when compared to uninfected controls. This response was partially stage-specific as a third of changes in mRNA abundance were either exclusively driven by one of the parasite forms or significantly different between them. Gene ontology analyses identified categories associated with immune functions (e.g. antigen presentation and leukocyte activation) among significantly downregulated mRNAs during amastigote infection while cytoprotective-related categories (e.g. DNA repair and apoptosis inhibition) were enriched in upregulated transcripts. Interestingly a combination of upregulated (e.g. cellular response to IFNβ) and repressed (e.g. leukocyte activation, chemotaxis) immune-related transcripts were overrepresented in the promastigote-infected dataset. In addition, Ingenuity Pathway Analysis (IPA) associated specific mRNA subsets with a number of upstream transcriptional regulators predicted to be modulated in macrophages infected with L. donovani amastigotes (e.g. STAT1 inhibition) or promastigotes (e.g. NRF2, IRF3, and IRF7 activation). Overall, our results indicate that early parasite stage-driven transcriptional remodelling in macrophages contributes to orchestrate both protective and deleterious host cell responses during L. donovani infection.

Assessing the susceptibility to permethrin and deltamethrin of two laboratory strains of Phlebotomus perniciosus from Madrid region, Spain.

Molina, R., Jiménez, M.
14-04-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35430262

Leishmania infantum is a protozoan causing cutaneous and visceral leishmaniasis in several regions of the world, including the Mediterranean basin. Phlebotomus perniciosus is one of the most important vectors of leishmaniasis in the countries of the western Mediterranean basin. Sand fly vector control by insecticides remains a useful tool in the framework of leishmaniasis control programs. Pyrethroids are the most widely used class of insecticides for sand fly control. There is currently a lack of information on the insecticide susceptibility and discriminating concentrations (DCs) of P. perniciosus. The aim of this study was to determine lethal concentrations (LC_{50}, LC_{95}, and LC_{99}) and DCs of deltamethrin and permethrin against two strains of P. perniciosus from Madrid region (Spain). According to WHO tube bioassay protocol 24-h mortality obtained after 1-h exposure to deltamethrin (0.0003%, 0.001%, 0.003%, 0.01%, 0.03%, and 0.1%) and permethrin (0.003%, 0.01%, 0.03%, 0.1%, 0.3%, and 1%) was recorded. The LC_{50}, LC_{95}, and LC_{99} as well as their respective 95% confidence intervals values were calculated from the baseline data using maximum probability estimates of parameters and binary logistic regression analysis (QCal software). The 100% mortality was recorded from 0.01% of

deltamethrin for both P. perniciosus strains and from 0.1% and 0.3% permethrin for Fuenlabrada and Boadilla strains, respectively. Final DCs of deltamethrin and permethrin of each P. perniciosus strain were determined based on setting this parameter at twice the minimum concentration of insecticide that kills 99% (LC_{99}) at the following percentages: Fuenlabrada strain (0.0582% deltamethrin and 0.2648% permethrin) and Boadilla strain (0.0406% deltamethrin and 0.2446% permethrin). The results indicate that both P. perniciosus strains are susceptible to deltamethrin and permethrin and can be used in susceptibility tests, although Boadilla strain offers more consistent results. Due to the scarce existing literature on insecticide DCs for sand flies and the different current procedures to determine their susceptibility to insecticides it is a priority to multiply efforts in order to develop standards for monitoring insecticide resistance in sand flies.

A standardized intraperitoneal Glucantime™ for experimental treatment of cutaneous leishmaniasis caused by Leishmania amazonensis in BALB/c mice.

Brustolin, A., Franzói, N., Ramos-Milaré, Á., Tanoshi, C., Mota, C., Demarchi, I., Lonardoni, M., Verzignassi Silveira, T.
12-04-2022
Exp Parasitol
https://pubmed.ncbi.nlm.nih.gov/35427563

Glucantime™ is the pentavalent antimony (Sb^{+5}) recommended as the first choice for treating cutaneous leishmaniasis (CL). It has been used as treatment control in animal studies to investigate new anti-Leishmania compounds. However, these studies have a range of Glucantime™ doses, different treatment times and routes of administration, and differing results. Our goal was to standardize intraperitoneal Glucantime™ treatment for CL in BALB/c mice infected with L. amazonensis. BALB/c mice were divided into six groups, with eight animals per group. The animals were infected with L. amazonensis and intraperitoneally treated with different doses of Sb^{+5} (20, 100 and 200 mg/kg/day) for 30 consecutive days. Healthy animals were used as negative infection and treatment control. Infected and untreated animals were used as positive infection control. Animals infected and treated with Ampho B were used as treatment control. Biochemical and histological analysis was performed to assess renal and liver toxicity. The parasite load in the popliteal lymph node, spleen and liver was determined by limiting dilution. Histological and collagen fiber analyses were performed on the lesions. Animals treated with Sb^{+5} 100 and 200 mg/kg/day showed a decreased paw measurements, associated with a reduction in the parasite load, with a clinical cure rate of 50% and 37.5%, respectively. These groups of animals also showed tissue regeneration and reduced inflammation. Animals treated with 100 mg/kg/day had collagen fiber parameters similar to those of the negative infection control. There were no biochemical signs of renal or liver toxicity in any of the groups. We found that Sb^{+5} 100 mg/kg/day was the lowest dose that showed effectiveness in treating CL in mice, and it may be a good model of treatment control in studies evaluating new treatments for CL in BALB/c mice.

Leishmania infantum infection serosurveillance in stray dogs inhabiting the Madrid community: 2007-2018.

Müller, A., Montoya, A., Escacena, C., de la Cruz, M., Junco, A., Iriso, A., Marino, E., Fúster, F., Miró, G.
14-04-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05226-6

Leishmaniosis is an endemic zoonotic disease in the Mediterranean basin caused by Leishmania infantum and transmitted by phlebotomine sandflies. While in dogs disease may be severe, leishmaniosis is also a public health concern as was shown in the largest outbreak of human leishmaniosis (HL) in Europe in 2009 occurring in the Madrid region. The aim of the present study was to assess the applicability of the Leishmaniosis Surveillance Program (LeishSP) established in Madrid in 1996 by examining trends in L. infantum seroprevalence and associated epidemiological risk factors based on data for the 2007-2018 period. The study population consisted of 3225 stray dogs from 17 animal shelters collaborating with the LeishSP. Seroprevalences were recorded twice annually (April and November) from 2007 to 2018. In each yearly period, a minimum of 100 dogs were tested to detect dogs infected before and after the sandfly risk season in Madrid area. Each dog was subjected to the same protocol of blood sample collection and clinical examination to collect epidemiological data and clinical signs. Anti-Leishmania-specific IgG was determined by IFAT cut-off≥1:100. Overall seroprevalence was 6.1% (198 positive dogs). Epidemiological data indicate a significantly higher seroprevalence in dogs > 4 years old, purebred dogs (Pit Bull and related breeds), and medium to large size dogs. There were no seroprevalence differences according to sex and/or season (April and November). In addition, no significant differences were observed according to whether dogs lived inside or outside the HL outbreak area. Remarkably, of 198 dogs testing positive for L. infantum, 64.6% had no clinical signs, indicating a high proportion of clinically healthy infected dogs that could be a potential source of infection. Results indicate a stable seroprevalence of L. infantum infection after 2006 in stray dogs in Madrid but with a recent slightly increasing trend. These observations support the need to continue with the LeishSP implemented by sanitary authorities of the Madrid Community as an early warning strategy for human and animal leishmaniosis and to enable continued assessment of the epidemiological role of dogs with subclinical infection in this important zoonotic disease.

The Leishmania donovani Ortholog of the Glycosylphosphatidylinositol Anchor Biosynthesis Cofactor PBN1 Is Essential for Host Infection.

Roberts, A., Nagar, R., Brandt, C., Harcourt, K., Clare, S., Ferguson, M., Wright, G.
14-04-2022

mBio
https://doi.org/10.1128/mbio.00433-22

Visceral leishmaniasis is a deadly infectious disease caused by Leishmania donovani, a kinetoplastid parasite for which no licensed vaccine is available. To identify potential vaccine candidates, we systematically identified genes encoding putative cell surface and secreted proteins essential for parasite viability and host infection. We identified a protein encoded by *LdBPK_061160* which, when ablated, resulted in a remarkable increase in parasite adhesion to tissue culture flasks. Here, we show that this phenotype is caused by the loss of glycosylphosphatidylinositol (GPI)-anchored surface molecules and that *LdBPK_061160* encodes a noncatalytic component of the L. donovani GPI-mannosyltransferase I (GPI-MT I) complex. GPI-anchored surface molecules were rescued in the *LdBPK_061160* mutant by the ectopic expression of both human genes *PIG-X* and *PIG-M*, but neither gene could complement the phenotype alone. From further sequence comparisons, we conclude that *LdBPK_061160* is the functional orthologue of yeast *PBN1* and mammalian *PIG-X*, which encode the noncatalytic subunits of their respective GPI-MT I complexes, and we assign *LdBPK_061160* as *LdPBN1*. The *LdPBN1* mutants could not establish a visceral infection in mice, a phenotype that was rescued by constitutive expression of *LdPBN1*. Although mice infected with the null mutant did not develop an infection, exposure to these parasites provided significant protection against subsequent infection with a virulent strain. In summary, we have identified the orthologue of the PBN1/PIG-X noncatalytic subunit of GPI-MT I in trypanosomatids, shown that it is essential for infection in a murine model of visceral leishmaniasis, and demonstrated that the *LdPBN1* mutant shows promise for the development of an attenuated live vaccine. IMPORTANCE Visceral leishmaniasis is a deadly infectious disease caused by the parasites Leishmania donovani and Leishmania infantum. It remains a major global health problem, and there is no licensed highly effective vaccine. Molecules that are displayed on the surface of parasites are involved in host-parasite interactions and have important roles in immune evasion, making vaccine development difficult. One major way in which parasite surface molecules are tethered to the surface is via glycophosphatidylinositol (GPI) anchors; however, the enzymes required for all the biosynthetic steps in these parasites are not known. Here, we identified the enzyme required for an essential step in the GPI anchor-biosynthetic pathway in L. donovani, and we show that while parasites lacking this gene are viable *in vitro*, they are unable to establish infections in mice, a property we show can be exploited to develop a live genetically attenuated parasite vaccine.

Survey on the presence of Leishmania sp. in peridomestic rodents from the Emilia-Romagna Region (North-Eastern Italy).

Magri, A., Galuppi, R., Fioravanti, M., Caffara, M.
12-04-2022
Vet Res Commun
https://doi.org/10.1007/s11259-022-09925-4

Leishmaniasis is a neglected vector-borne parasitic disease caused in Italy only by the species Leishmania infantum of the Leishmania donovani complex, which is the causative agent of the zoonotic visceral leishmaniasis (VL) and the sporadic cutaneous leishmaniasis (CL) in humans, and of the canine leishmaniasis (CanL). The disease is considered endemic in southern, central, and insular Italian regions and recognizes phlebotomine sand flies as vector and dogs as main reservoir. Among northern Italian region, Emilia-Romagna shows peculiar epidemiological situation and recent studies are questioning the role of dog as main reservoir of L. infantum. Due to their synanthropic relationship with humans, rodents have been tested for Leishmania spp. in several European countries. The aim of this study was to assess the presence of Leishmania spp. in peridomestic rodents in the Emilia-Romagna. The study was carried out on 136 peridomestic rodents collected by professional pest control services: 47 brown rats (Rattus norvegicus), 39 black rats (Rattus rattus) and 50 mice (Mus musculus). Specimens of earlobe skin, spleen, liver and prescapular lymph nodes were tested with a real-time PCR. Fifteen (11%) rodents, tested positive for Leishmania spp. in particular five brown rats (10.6%), five black rats (12.8%) and five mice (10%). Positivity was obtained from different target organs. These findings revealed the presence of Leishmania spp. in peridomestic rodents of Emilia-Romagna Region, also in two species never tested before in Italy, namely R. norvegicus and M. musculus.

Effects of anti-Leishmania compounds in the behavior of the sand fly vector Lutzomyia longipalpis.

Ferreira, T., Brazil, R., McDowell, M., Cunha-Júnior, E., Costa, P., Netto, C., Santos, E., Genta, F.
12-04-2022
Pest Manag Sci
https://doi.org/10.1002/ps.6900

Leishmaniasis is an infectious parasitic disease caused by pathogens of the genus Leishmania transmitted through the bite of adult female sand flies. To reduce case numbers, it is necessary to combine different control approaches, especially those aimed at the sand fly vectors. Innovative forms of control with the use of attractive sugar baits explored the fact that adult sand flies need to feed on sugars of plant origin. Leishmania parasites develop in the gut of sand flies, interacting with the sugars in the diet of adults. Recent studies have shown that sugar baits containing plant-derived compounds can reduce sand fly survival, the number of parasites per gut, and the percentage of infected sand flies. Several synthetic compounds produced from naphthoquinones and pterocarpans have anti-parasitic activity on L. amazonensis and/or L. infantum in cell culture. This work aimed to assess the inclusion of these compounds in sugar baits for blocking transmission, targeting the development of the Leishmania parasite inside the sand fly vector. We evaluated the attractant or repellent properties of these

compounds, as well as of the reference compound DEET, in sugar baits. We also observed changes in feeding preference caused by these compounds, looking for anti-feeding or stimulation of ingestion. Pterocarpanquinone L4 and pentamidine showed attractant and repellent properties, respectively. Based on the effects in feeding preference and intake volume, pterocarpanquinone L6, and the pyrazole-derived compound P8 were chosen as the most promising compounds for the future development of anti-Leishmania sugar baits.

Hyaluronic acid-amphotericin B nanocomplexes: a promising anti-leishmanial drug delivery system.

Silva-Carvalho, R., Leão, T., Bourbon, A., Gonçalves, C., Pastrana, L., Parpot, P., Amorim, I., Tomás, A., Gama, F.
12-04-2022
Biomater Sci
https://doi.org/10.1039/d1bm01769a

The development of an effective amphotericin B (AmB) formulation to replace actual treatments available for leishmaniasis, which present serious drawbacks, is a challenge. Here we report the development of hyaluronic acid-amphotericin B self-assembled nanocomplexes (HA-AmB), processed by freeze-drying (FD) or nano spray-drying (SD), using a simple process that favors the non-covalent drug-polysaccharide association in an amorphous state. These water-soluble formulations, which presented a nanometric size (300-600 nm), high colloidal stability (zeta potential around -39 mV) and an AmB loading (15-18%) in aggregated and super aggregated states, demonstrated less *in vitro* cytotoxic and hemolytic effects compared to the free-drug. A significant decrease in the number of intramacrophagic *L. infantum* amastigotes upon treatment (IC_{50} of 0.026 and 0.030 µM for HA-AmB FD and HA-AmB SD, respectively) was also observed, and the best selectivity index (SI) was observed for the HA-AmB SD nanocomplex (SI of 651). Intravenous administration of the HA-AmB SD nanocomplex for 3 alternate days showed an effective parasite reduction in the spleen and liver of C57BL/6 mice without signs of toxicity commonly observed upon free-AmB treatment. Although lower than that achieved with AmBisome® in the liver, the observed parasite reduction for the nanocomplex was of a similar order of magnitude. The efficacy, stability, safety and low cost of the HA-AmB SD nanocomplex highlight its potential as an alternative treatment for leishmaniasis.

Carboxymethyl chitosan modified lipid nanoformulations as a highly efficacious and biocompatible oral anti-leishmanial drug carrier system.

Singh, A., Yadagiri, G., Negi, M., Kushwaha, A., Singh, O., Sundar, S., Mudavath, S.
08-02-2022
Int J Biol Macromol
https://pubmed.ncbi.nlm.nih.gov/35149096

Herein, carboxymethyl chitosan (CMC) grafted lipid nanoformulations were facilely prepared by thin-film hydration method as a highly efficient biocompatible anti-leishmanial carrier encapsulating amphotericin B (AmB). Nanoformulations were characterized for their physicochemical characteristics wherein TEM analysis confirmed the spherical structure, whereas FTIR analysis revealed the conjugation of CMC onto nanoformulations and confirmed the free state of AmB. Furthermore, the wettability study confirmed the presence of CMC on the surface of nanoformulations attributed to the enhanced hydrophilicity. Surface hydrophilicity additionally contributes towards consistent mucin retention ability for up to 6 h, superior mucoadhesiveness, and hence enhanced bioavailability. The proposed nanoformulations with high encapsulation and drug loading properties displayed controlled drug release in the physiological microenvironment. In vitro, antileishmanial results showed an astounding 97% inhibition in amastigote growth. Additionally, in vivo studies showed that treatment with nanoformulations significantly reduced the liver parasitic burden (93.5%) without causing any toxicity when given orally.

Sodium stibogluconate and CD47-SIRPα blockade overcome resistance of anti-CD20-opsonized B cells to neutrophil killing.

van Rees, D., Brinkhaus, M., Klein, B., Verkuijlen, P., Tool, A., Schornagel, K., Treffers, L., van Houdt, M., Kater, A., Vidarsson, G., Gennery, A., Kuijpers, T., van Bruggen, R., Matlung, H., van den Berg, T.
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Blood Adv
https://doi.org/10.1182/bloodadvances.2021005367

Anti-CD20 antibodies such as rituximab are broadly used to treat B-cell malignancies. These antibodies can induce various effector functions, including immune cell-mediated antibody-dependent cellular cytotoxicity (ADCC). Neutrophils can induce ADCC toward solid cancer cells by trogoptosis, a cytotoxic mechanism known to be dependent on trogocytosis. However, neutrophils seem to be incapable of killing rituximab-opsonized B-cell lymphoma cells. Nevertheless, neutrophils do trogocytose rituximab-opsonized B-cell lymphoma cells, but this only reduces CD20 surface expression and is thought to render tumor cells therapeutically resistant to further rituximab-dependent destruction. Here, we demonstrate that resistance of B-cell lymphoma cells toward neutrophil killing can be overcome by a combination of CD47-SIRPα checkpoint blockade and sodium stibogluconate (SSG), an anti-leishmaniasis drug and documented inhibitor of the tyrosine phosphatase SHP-1. SSG enhanced neutrophil-mediated ADCC of solid tumor cells but enabled trogoptotic killing of B-cell lymphoma cells by turning trogocytosis from a mechanism that contributes to resistance into a cytotoxic anti-cancer mechanism. Tumor cell killing in the presence of SSG required both antibody opsonization of the target cells and disruption of CD47-SIRPα interactions. These results provide a more detailed understanding of the role of neutrophil

trogocytosis in antibody-mediated destruction of B cells and clues on how to further optimize antibody therapy of B-cell malignancies.

CYSTICERCOSE

DRACUNCULOSE

ECHINOCOCCOSE

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

Effect of primary and secondary Fasciola gigantica infection on specific IgG responses, hepatic enzyme levels and weight gain in buffaloes.

Wang, J., He, K., Wang, Z., Wen, C., Han, X., Meng, Z., Yuan, X., Wu, Z., Zhang, W., Di, W.
13-04-2022
Parasitol Res
https://doi.org/10.1007/s00436-022-07519-2

Buffaloes, as highly susceptible definitive hosts of Fasciola gigantica, suffer from a high infection rate of fasciolosis, which causes enormous economic losses. Repeat infection is responsible for this high rate; thus, elucidating the protective immunity mechanism in repeat infection is decisive in fasciolosis prevention. Herein, a secondary experimental infection model was established to preliminarily reveal the protective immunity that occurs in repeat infection. In brief, animals were assigned to three groups: group A (uninfected control), group B (primary infection) and group C (secondary infection). Buffaloes were autopsied 20 weeks post-infection for measurements of the recovered flukes and hepatic examination. In addition, the detection of specific antibody (IgG) responses to F. gigantica excretory-secretory product (FgESP) throughout the whole period and weight gain throughout the first 4 months as a percentage (%) of the starting weight were also determined. The serum hepatic enzyme gamma glutathione transferase (GGT) levels were monitored to assess hepatic damage throughout the study period. Infection establishment was compared between group B and group C. Similar specific IgG patterns were observed between group B and group C, and hepatic damage was more severe in group C than group B. Significant differences in weight gain as a percentage of the start weight were observed between group A and group B at the 3rd and 4th months postprimary infection, while significant differences were not observed between group A and group C or group B and group C. Our results suggest that challenge infection cannot induce resistance against F. gigantica in buffaloes, which is consistent with the protective immunity against Fasciola hepatica reinfection observed in sheep and goats.

FILARIOSE LYMPHATIQUE

MYCETOME

ONCHOCERCOSE

SCHISTOSOMIASE

Human umbilical cord blood mesenchymal stem cells as a potential therapy for schistosomal hepatic fibrosis: an experimental study.

Abou Rayia, D., Ashour, D., Abo Safia, H., Abdel Ghafar, M., Amer, R., Saad, A.
18-04-2022
Pathog Glob Health
https://doi.org/10.1080/20477724.2022.2064795

The objective of our study was to assess the effect of human umbilical cord blood (HUCB) mesenchymal stem cells (MSCs) transplantation on schistosomal hepatic fibrosis in mice. The study animals were divided into three groups. Group I is a control group, where the mice were infected with *Schistosoma mansoni* cercariae and remained untreated. The mice of the other two groups were infected and treated with either praziquantel (Group II) or HUCB-MSCs (Group III). Liver function tests, as well as histopathological evaluation of liver fibrosis using hematoxylin and eosin and Masson's trichrome stains, were performed. Additionally, an immunohistochemical study was carried out using anti-glial fibrillary acidic protein (GFAP) in hepatic stellate cells. Compared to the control group, the treated (praziquantel and MSCs) groups showed a substantial improvement, with a

significant difference regarding the histopathological evaluation of liver fibrosis in the MSCs-treated group. In conclusion, MSCs could be a promising and efficient cell therapy for liver fibrosis.

Performance of loop-mediated isothermal amplification (LAMP) for detection of *Schistosoma mansoni* infection compared with Kato-Katz and real-time PCR.

Allam, A., Kamel, M., Farag, H., Raheem, H., Shehab, A., Hagras, N.
18-04-2022
J Helminthol
https://doi.org/10.1017/S0022149X22000153

The performance of loop-mediated isothermal amplification (LAMP) for detection of Schistosoma mansoni DNA from stool and urine samples in comparison with Kato-Katz and real-time polymerase chain reaction (PCR) was studied. After obtaining informed consent, 50 children participated in the present study and agreed to submit stool and urine samples. Stool samples were examined by Kato-Katz. Both real-time PCR and LAMP techniques were applied on stool and urine samples. The overall prevalence of S. mansoni was 46% in stool and urine samples as detected by the employed techniques, and 90% of cases had light infection intensity. The highest percentage of infection was diagnosed by real-time PCR (44%), followed by Kato-Katz (42%) and LAMP in the stool (36%), while the lowest percentages of infection were diagnosed by real-time PCR and LAMP in urine samples (24% and 14%, respectively). Kato-Katz, real-time PCR and LAMP showed 100% specificity where the sensitivity was 91.3%, 95.7% and 78.3%, respectively, in stool samples. Real-time PCR and LAMP showed lower sensitivity in urine samples. The LAMP assay is a promising technique for S. mansoni diagnosis in endemic countries of moderate and high-intensity infection. Yet, it needs further optimization, particularly in urine samples.

Emerging roles for extracellular vesicles in Schistosoma infection.

Revue de littérature

Abou-El-Naga, I.
12-04-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35427535

The co-evolution of Schistosoma and its host necessitates the use of extracellular vesicles (EVs) generated by different lifecycle stages to manipulate the host immune system to achieve a delicate balance between the survival of the parasite and the limited pathology of the host. EVs are phospholipid bilayer membrane-enclosed vesicles capable of transferring a complex mixture of proteins, lipids, and genetic materials to the host. They are nano-scale-sized vesicles involved in cellular communication. In this review, the author summarized the proteins involved in the biogenesis of schistosome-derived EVs and their cargo load. miRNAs are one cargo molecule that can underpin EVs functions and significantly affect parasite/host interactions and immune modulation. They skew macrophage polarization towards the M1 phenotype and downregulate Th2 immunity. Schistosoma can evade the host immune system's harmful effects by utilizing this strategy. In order to compromise the protective effect of Th2, EVs upregulate T regulatory cells and activate eosinophils, which contribute to granuloma formation. Schistosomal EVs also affect fibrosis by acting on non-immune cells such as hepatic stellate cells. These vesicles drew attention to translational applications in diagnosis, immunotherapy, and potential vaccines. A deep understanding of the interaction of schistosome-derived EVs with host cells will significantly increase our knowledge about the dynamics between the host and the worm that may aid in controlling this debilitating disease.

Experimental Schistosoma japonicum-induced pulmonary hypertension.

Kassa, B., Lee, M., Kumar, R., Mickael, C., Sanders, L., Tuder, R., Mentink-Kane, M., Graham, B.
13-04-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010343

Schistosomiasis, a major cause of pulmonary arterial hypertension (PAH) worldwide, is most clearly described complicating infection by one species, Schistosoma mansoni. Controlled exposure of mice can be used to induce Type 2 inflammation-dependent S. mansoni pulmonary hypertension (PH). We sought to determine if another common species, S. japonicum, can also cause experimental PH. Schistosome eggs were obtained from infected mice, and administered by intraperitoneal sensitization followed by intravenous challenge to experimental mice, which underwent right heart catheterization and tissue analysis. S. japonicum sensitized and challenged mice developed PH, which was milder than that following S. mansoni sensitization and challenge. The degree of pulmonary vascular remodeling and Type 2 inflammation in the lungs was similarly proportionate. Cross-sensitization revealed that antigens from either species are sufficient to sensitize for intravenous challenge with either egg, and the degree of PH severity depended on primarily the species used for intravenous challenge. Compared to a relatively uniform distribution of S. mansoni eggs, S. japonicum eggs were observed in clusters in the lungs. S. japonicum can induce experimental PH, which is milder than that resulting from comparable S. mansoni exposure. This difference may result from the distribution of eggs in the lungs, and is independent of which species is used for sensitization. This result is consistent with the clearer association between S. mansoni infection and the development of schistosomiasis-associated PAH in humans.

Real-time and automated monitoring of antischistosomal drug activity profiles for screening of compound libraries.

Ravaynia, P., Biendl, S., Grassi, F., Keiser, J., Hierlemann, A., Modena, M.
16-03-2022
iScience
https://doi.org/10.1016/j.isci.2022.104087

Schistosomiasis is a neglected tropical disease that affects over 200 million people annually. As the antischistosomal drug pipeline is currently empty, repurposing of compound libraries has become a source for accelerating drug development, which demands the implementation of high-throughput and efficient screening strategies. Here, we present a parallelized impedance-based platform for continuous and automated viability evaluation of *Schistosoma mansoni* schistosomula in 128 microwells during 72 h to identify antischistosomal hits *in vitro*. By initially screening 57 repurposed compounds against larvae, five drugs are identified, which reduce parasite viability by more than 70%. The activity profiles of the selected drugs are then investigated via real-time dose-response monitoring, and four compounds reveal high potency and rapid action, which renders them suitable candidates for follow-up tests against adult parasites. The study shows that our device is a reliable tool for real-time drug screening analysis of libraries to identify new promising therapeutics against schistosomiasis.

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

A novel rapid visual detection assay for Toxoplasma gondii combining recombinase-aided amplification and lateral flow dipstick coupled with CRISPR-Cas13a fluorescence (RAA-Cas13a-LFD).

Zhao, J., Li, Y., Xue, Q., Zhu, Z., Zou, M., Fang, F.
14-04-2022
Parasite
https://doi.org/10.1051/parasite/2022021

Toxoplasmosis, a parasitic disease resulting from Toxoplasma gondii infection, remains prevalent worldwide, and causes great harm to immunodepressed patients, pregnant women and newborns. Although various molecular approaches to detect T. gondii infection are available, they are either costly or technically complex. This study aimed at developing a rapid visual detection assay using recombinase-aided amplification (RAA) and lateral flow dipstick (LFD) coupled with CRISPR-Cas13a fluorescence (RAA-Cas13a-LFD) to detect T. gondii. The RAA-Cas13a-LFD assay was performed in an incubator block at 37 °C within 2 h, and the amplification results were visualized and determined through LFD by the naked eye. The detection limit was 1×10^{-6} ng/μL by our developed RAA-Cas13a-LFD protocol, 100-fold higher than that by qPCR assay (1×10^{-8} ng/μL). No cross-reaction occurred either with the DNA of human blood or Ascaris lumbricoides, Digramma interrupta, Entamoeba coli, Fasciola gigantica, Plasmodium vivax, Schistosoma japonicum, Taenia solium, and Trichinella spiralis, and the positive rate by RAA-Cas13a-LFD assay was identical to that by qPCR assay (1.50% vs. 1.50%) in detecting T. gondii infection in the unknown blood samples obtained from clinical settings. Our findings demonstrate that this RAA-Cas13a-LFD assay is not only rapid, sensitive, and specific and allows direct visualization by the naked eye, but also eliminates sophisticated and costly equipment. More importantly, this technique can be applied to on-site surveillance of T. gondii.

GALE

Oral Albendazole as an Alternative Treatment for Moderate Crusted Scabies Along with 5% Permethrin and 5% Salicylic Acid.

Gunawan, H., Banjarnahor, I., Achdiat, P.
12-04-2022
Int Med Case Rep J
https://doi.org/10.2147/IMCRJ.S359928

Crusted scabies (CS) is a severe variant of scabies, highly contagious, caused by numerous *Sarcoptes scabiei (S. scabiei*) infestation. CS is associated with immunosuppressive conditions, like systemic lupus erythematosus (SLE). Various topical and oral scabicidals are used in the treatment of CS, including topical sulfur compounds, benzyl benzoate, crotamiton, lindane, malathion, permethrin, and ivermectin. The treatment of CS does not only need scabicidals, but also keratolytic agents to remove the thick crusts. The severity of CS is classified into three levels and related to the dose of oral ivermectin treatment. When oral ivermectin is not available, oral albendazole can be used as an alternative treatment. A case of CS in a 21-year-old girl with SLE was reported. Physical examination showed multiple lesions in the form erythematous papules, plaques, scales, and hyperkeratotic crusts in almost all parts of the body. The distribution of crusting >30% body surface area, the depth of crusting >10 mm, and there were pyoderma. Sarcoptes scabiei, eggs, and scybala were found on skin scraping. The patient was diagnosed as a moderate CS and treated with occlusive dressings using 5% salicylic acid in vaseline until crusts fell off, 5% permethrin cream three times per week, and 800 mg/day albendazole three consecutive days per week. A clinical and microscopic cure was achieved at day 19 of observation. Albendazole is an antiprotozoal agent with larvicidal effect, therefore it can be used as an alternative treatment of CS when oral ivermectin is unavailable, along with 5% permethrin and 5% salicylic acid.

RF - Scabies Outbreak During the COVID-19 Lockdown.

Cerro, P., Navarro-Bielsa, A., Palma, A.
15-04-2022
Actas Dermosifiliogr
https://pubmed.ncbi.nlm.nih.gov/35436487

MORSURES DE SERPENT

Response to Letter to the Editor Regarding 'Crotalidae Polyvalent Immune Fab (CroFab®) and Cost-Effective Management of Hospital Admissions for Snakebites'.

Bowden, M., Christie, D.
11-04-2022
Am Surg
https://doi.org/10.1177/00031348221087928

Initial Experience with F(ab')2 Antivenom Compared with Fab Antivenom for Rattlesnake Envenomations Reported to a single poison center during 2019.

Wilson, B., Bahadir, A., Andrews, M., Karpen, J., Winkler, G., Smelski, G., Dudley, S., Walter, F., Shirazi, F.
24-01-2022
Toxicon
https://pubmed.ncbi.nlm.nih.gov/35085602

There are two Food and Drug Administration (FDA)-approved antivenoms available for rattlesnake envenomations in the United States: the equine-derived F (ab')2 product sold with the brand name Anavip (F (ab')2 AV) and the ovine-derived Fab product sold with the brand name Crofab (FabAV). To compare the clinical outcomes of rattlesnake envenomation patients treated either with FabAV or F (ab')^{2}AV or a combination of these. This is a retrospective chart review of all human rattlesnake envenomations requiring antivenom reported to one regional poison control center in 2019. Patients were categorized as receiving F (ab')2 AV, FabAV, or a combination of both. Baseline characteristics included demographics, time between envenomation and administering antivenom, an abbreviated snakebite severity score (ASSS), and the presence of coagulopathy at presentation. There were a total of 123 patients requiring antivenom. Of these, 57 (46.3%) received FabAV, 53 (43.1%) received F (ab')2 AV, and 13 (10.6%) received a combination of these. Those receiving F (ab')2 AV were younger, with an average age of 40.8 (±25.0) years versus 51.3 (±19.9) years (p = 0.0161) for those receiving FabAV. Time between envenomation and antivenom administration, ASSS, and the percentage of those with coagulopathy at presentation were otherwise similar. Patients treated with F (ab')2 AV or FabAV received a similar total number of vials [16.0 vials (±6.1) vs 14.5 vials (±5.4), p = 0.189], but patients treated with F (ab')2 AV were more frequently given additional doses [31 patients (58.5%) vs. 22 FabAV patients (38.6%), p = 0.0051]. In patients with outpatient follow-up for 2 weeks, fewer patients treated with F (ab')2 AV developed late coagulopathy [5 patients (11.1%) vs 22 FabAV patients (48.9%), p = 0.0004]. Adverse events were generally mild and uncommon with no difference in frequency between patients who received either antivenom (2 F (ab')2 AV patients vs 4 FabAV patients, p = 0.6637). Other than patient age, we found no significant difference in the baseline demographics, time between envenomation and administering antivenom, an abbreviated snakebite severity score (ASSS), and the presence of coagulopathy at presentation between patients receiving F (ab')2 AV or FabAV. Patients receiving F (ab')2 AV were more likely to be given an additional dose beyond the minimum typical treatment course, but less likely to develop late coagulopathy. Adverse events were uncommon and generally mild whether patients received either antivenom.