Réseau MTN Francophone

# Veille scientifique
# Maladies tropicales négligées

## Semaine 24

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# DENGUE, CHIKUNGUNYA ET MALADIE A VIRUS ZIKA

## Dengue Infection Immediately After Kidney Transplantation.

**Bansal, S., Rana, A., Gadde, A., Jha, P., Kotton, C.**
17-06-2022
*Transplantation*
https://doi.org/10.1097/TP.0000000000004124

## Dengue in the cooling off period of the COVID-19 epidemic in Brazil: from the shadows to the spotlight.

**Souza, C., Romano, C.**
17-06-2022
*Rev Inst Med Trop Sao Paulo*
https://pubmed.ncbi.nlm.nih.gov/35730870

## Plants extracts from Cameroon pharmacopeia strongly inhibit the Chikungunya virus infection by targeting entry and replication steps.

**Simo Nemg, F., De, S., Keshry, S., Mamidi, P., Njayou, F., Demanou, M., Moundipa Fewou, P., Chattopadhyay, S.**
18-06-2022
*J Ethnopharmacol*
https://pubmed.ncbi.nlm.nih.gov/35728708

Ethnopharmacological relevance: Cameroon is one of the sub-Saharan African countries affected by Chikungunya virus (CHIKV). With the absence of approved treatment, this disease represents globally a major public health concern. Several plants are traditionally used in Cameroon for the treatment of virus induced fever and arthralgia. But to date there is no study that validate the efficacy of these plants for the treatment of Chikungunya virus infection. Aim of the study: This study aims to explore the inhition effect, mechanism of action of plant extracts against Chikungunya virus. Material and methods: An ethnobotanical survey conducted in some regions of Cameroon, led to the identification of nine medicinal plants used in traditional medicine for the healing of fever-related diseases and arthritis. Crude hydro-ethanolic extracts of each plant were prepared by maceration and their effects against CHIKV infection were investigated. CHIKV S27 strain was used to infection in Vero cell line. The antiviral activities were determined by plaque assay and/or RT-PCR targeting E1 envelope gene of CHIKV. Dose-response studies of the active plants were also determined by flow cytometry and Western blot. Results: Four extracts, Entada africana Guill et Pers. (E4), Entandrophragma cylindricum Sprague (EI), Khaya grandifoliola C. D.C. Sapindales (E2) and Macaranga hurifolia Beille (E6) showed antiviral activity with the half-maximal inhibitory concentration of 8.29; 8.14; 12.81 and 26.89 µg/mL respectively. All extracts were nontoxic up to the concentration of 100 µg/µL. Entandrophragma cylindricum Sprague (EI), Khaya grandifoliola C. D.C. Sapindales (E2), and Entada africana Guill et Pers. (E4) showed strong inhibition on the entry step of viral infection. At the same time, only Entandrophragma cylindricum Sprague (EI) inhibited the viral titer significantly in replication and intercellular assembly steps. Four plant extracts namely Entandrophragma cylindricum Sprague (EI), Macaranga hurifolia Beille (E6), Phragmentera capitata (Sprengel) Balle (E12), and Detarium microcarpum (E13) were effective against egression step. Conclusions: Together, the results of this study showed anti-chikungunya activities of Entandrophragma cylindricum Sprague (EI) and Macaranga hurifolia Beille (E6), with therapeutics perspectives and can be promising sources of the development of anti-CHIKV molecule in future.

## Systematic Review of the Serotonergic System in the Pathophysiology of Severe Dengue: The Theory of Thrombocytopenia and Vascular Extravasation.

**Corzo-Gómez, J., Picazo, O., Castellanos-Pérez, M., Briones-Aranda, A.**
19-06-2022
*Mini Rev Med Chem*
https://doi.org/10.2174/1389557522666220619231643

Background: Severe dengue is characterized by thrombocytopenia, hemorrhaging, and/or capillary extravasation, and may be linked to a reduced plasma concentration of serotonin (5-hydroxytriptamine, or 5-HT). Objective: The aim of the current contribution was to conduct a systematic bibliographic review of reports on the role of the peripheral serotonergic system in the pathophysiology of severe dengue. Methods: A bibliographic review was carried out of in vivo/in vitro models, clinical trials, and case series studies from 2010-2019. The selective criteria were the use of treatments with serotonin reuptake inhibitors and/or agonists/antagonists of 5-HT receptors, and their impact on inflammation, coagulation, and the endothelium. Also included were cross-sectional and cohort studies on the relationship between intraplatelet and plasma 5-HT levels in patients with dengue. The risk of bias in the selected reports was examined with domain-based assessment utilizing Cochrane-type criteria. The main results are summarized in tables and figures. Results: Based on descriptions of the effect of serotonergic drugs on 5-HT levels and the findings of clinical trials of dengue treatment, most receptors of the peripheral serotonergic system, and especially 5-HT2A, seem to participate in regulating serum 5-HT during severe dengue. Therefore, the peripheral serotonergic system probably contributes to thrombocytopenia and capillary extravasation. Conclusion: Regarding dengue, 5-HT may be a key parameter for predicting severity, and an understanding of 5-HT-related mechanisms could possibly facilitate the development of new therapies. These proposals require further research due to the limited number of publications on the role of serotonergic receptors at the peripheral level. 320222.

## N$^6$-methyladenosine modification of the Aedes aegypti transcriptome and its alteration upon dengue virus infection in Aag2 cell line.

**Dai, Z., Etebari, K., Asgari, S.**
20-06-2022
*Commun Biol*
https://doi.org/10.1038/s42003-022-03566-8

The N$^6$-methyladenosine (m$^6$A) modification of RNA has been reported to affect viral infections. Studies have confirmed the role of m$^6$A in replication of several vector-borne flaviviruses, including dengue virus (DENV), in mammalian cells. Here, we explored the role of m$^6$A in DENV replication in the mosquito Aedes aegypti Aag2 cell line. We first determined the presence of m$^6$A on the RNAs from mosquito cells and using methylated RNA immunoprecipitation and sequencing (MeRIP-Seq) identified m$^6$A modification of the mosquito transcriptome and those that changed upon DENV infection. Depletion of m$^6$A methyltransferases and the m$^6$A binding protein YTHDF3 RNAs decreased the replication of DENV. In particular, we found that the Ae. aegypti ubiquitin carrier protein 9 (Ubc9) is m$^6$A modified and its expression increases after DENV infection. Silencing of the gene and ectopic expression of Ubc9 led to reduced and increased DENV replication, respectively. The abundance of Ubc9 mRNA and its stability were reduced with the inhibition of m$^6$A modification, implying that m$^6$A modification of Ubc9 might enhance expression of the gene. We also show that the genome of DENV is m$^6$A modified at five sites in mosquito cells. Altogether, this work reveals the involvement of m$^6$A modification in Ae. aegypti-DENV interaction.

## A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for an inactivated viral vaccine against Chikungunya virus.

**Hernandez, L., Sumathy, K., Sahastrabuddhe, S., Excler, J., Kochhar, S., Smith, E., Gurwith, M., Chen, R., Benefit-Risk Assessment of VAccines by TechnolOgy Working Group (BRAVATO, ex-V3SWG)**
14-06-2022
*Vaccine*
https://pubmed.ncbi.nlm.nih.gov/35715351

Inactivated viral vaccines have long been used in humans for diseases of global health threat (e.g., poliomyelitis and pandemic and seasonal influenza) and the technology of inactivation has more recently been used for emerging diseases such as West Nile, Chikungunya, Ross River, SARS and especially for COVID-19. The Brighton Collaboration Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) Working Group has prepared standardized templates to describe the key considerations for the benefit and risk of several vaccine platform technologies, including inactivated viral vaccines. This paper uses the BRAVATO inactivated virus vaccine template to review the features of an inactivated whole chikungunya virus (CHIKV) vaccine that has been evaluated in several preclinical studies and clinical trials. The inactivated whole CHIKV vaccine was cultured on Vero cells and inactivated by ß-propiolactone. This provides an effective, flexible system for high-yield manufacturing. The inactivated whole CHIKV vaccine has favorable thermostability profiles, compatible with vaccine supply chains. Safety data are compiled in the current inactivated whole CHIKV vaccine safety database with unblinded data from the ongoing studies: 850 participants from phase II study (parts A and B) outside of India, and 600 participants from ongoing phase II study in India, and completed phase I clinical studies for 60 subjects. Overall, the inactivated whole CHIKV vaccine has been well tolerated, with no significant safety issues identified. Evaluation of the inactivated whole CHIKV vaccine is continuing, with 1410 participants vaccinated as of 20 April 2022. Extensive evaluation of immunogenicity in humans shows strong, durable humoral immune responses.

## Congenital Zika syndrome and living conditions in the largest city of northeastern Brazil.

**Souza, M., da Natividade, M., Werneck, G., Dos Santos, D.**
20-06-2022
*BMC Public Health*
https://doi.org/10.1186/s12889-022-13614-x

**Background:** The Zika virus (ZIKV) epidemic hit Brazil in 2015 and resulted in a generation of children at risk of congenital Zika syndrome (CZS). The social vulnerability of certain segments of the population contributed to the disproportional occurrence of CZS in the Brazilian Northeast, the poorest region in the country. Living conditions are essential factors in understanding the social determination of CZS, which is embedded in a complex interaction between biological, environmental, and social factors. Salvador, the biggest city in the region, played a central role in the context of the epidemic and was a pioneer in reporting the ZIKV infection and registering a high number of cases of CZS. The aim of the study was identifying the incidence and spatial distribution pattern of children with CZS in the municipality of Salvador, according to living conditions. **Methods:** This is an ecological study that uses the reported cases of ZIKV and CZS registered in the epidemiological surveillance database of the Municipal Secretariat of Health of the city of Salvador between August of 2015 and July of 2016. The neighborhoods formed the analysis units and the thematic maps were built based on the reported cases. Associations between CZS and living conditions were assessed using the Kernel ratio and a spatial autoregressive linear regression model. **Results:** Seven hundred twenty-six live births were reported, of which 236 (32.5%) were confirmed for CZS. Despite the reports of ZIKV infection being widely distributed, the cases of CZS were concentrated in poor areas of the city. A positive spatial association was observed between living in places with poorer living conditions and births of children with CZS. **Conclusions:** This study shows the role of living conditions in the occurrence of births of children with CZS and indicates the need for approaches that recognize the part played by social inequalities in determining CZS and in caring for the children affected.

## Structural dynamics of Zika virus NS1 via a reductionist approach reveal the disordered nature of its β-roll domain in isolation.

**Kapuganti, S., Kumar, P., Giri, R.**
14-06-2022
*Virology*
https://pubmed.ncbi.nlm.nih.gov/35724498

Flavivirus Non-structural 1 (NS1) protein performs multiple functions and it is highly plausible that significant structural and folding dynamics of NS1 might play a role in its multifunctionality. It is important to understand the structural conformations of NS1 and its domains in isolation, possibly highlighting the implications on the overall NS1 protein dynamics. Therefore, we have employed extensively long molecular dynamic (MD) simulations in understanding the dynamics of the three structural domains (i.e., β-roll, wing, and β-ladder) in isolation, as a reductionist approach. We also found that the β-ladder domain is highly flexible, while the β-roll domain is disordered during long simulations. Further, we experimentally validated our findings using CD spectroscopy and confirmed the intrinsically disordered behavior of NS1 β-roll in isolation and lipid mimetic environments. Therefore, we believe this study may have implications for significant dynamics played by NS1 protein, specifically during oligomerization of NS1.

## Animal venoms as a source of antiviral peptides active against arboviruses: a systematic review.

Revue de littérature

**Lima, W., Maia, C., de Carvalho, T., Leite, G., Brito, J., Godói, I., de Lima, M., Ferreira, J.**
20-06-2022
*Arch Virol*
https://doi.org/10.1007/s00705-022-05494-8

Arthropod-borne viruses (arboviruses), such as Zika virus (ZIKV), chikungunya virus (CHIKV), dengue virus (DENV), yellow fever virus (YFV), and West Nile virus (WNV), are pathogens of global importance. Therefore, there has been an increasing need for new drugs for the treatment of these viral infections. In this context, antimicrobial peptides (AMPs) obtained from animal venoms stand out as promising compounds because they exhibit strong antiviral activity against emerging arboviral pathogens. Thus, we systematically searched and critically analyzed in vitro and in vivo studies that evaluated the anti-arbovirus effect of peptide derivatives from toxins produced by vertebrates and invertebrates. Thirteen studies that evaluated the antiviral action of 10 peptides against arboviruses were included in this review. The peptides were derived from the venom of scorpions, spiders, wasps, snakes, sea snails, and frogs and were tested against DENV, ZIKV, YFV, WNV, and CHIKV. Despite the high structural variety of the peptides included in this study, their antiviral activity appears to be associated with the presence of positive charges, an excess of basic amino acids (mainly lysine), and a high isoelectric point (above 8). These peptides use different antiviral mechanisms, the most common of which is the inhibition of viral replication, release, entry, or fusion. Moreover, peptides with virucidal and cytoprotective (pre-treatment) effects were also identified. In conclusion, animal-venom-derived peptides stand out as a promising alternative in the search and development of prototype antivirals against arboviruses.

## Acute neurologic emerging flaviviruses.

Revue de littérature

**Caldwell, M., Boruah, A., Thakur, K.**
13-06-2022
*Ther Adv Infect Dis*
https://doi.org/10.1177/20499361221102664

The COVID-19 pandemic has shed light on the challenges we face as a global society in preventing and containing emerging and re-emerging pathogens. Multiple intersecting factors, including environmental changes, host immunological factors, and pathogen dynamics, are intimately connected to the emergence and re-emergence of communicable diseases. There is a large and expanding list of communicable diseases that can cause neurological damage, either through direct or indirect routes. Novel pathogens of neurotropic potential have been identified through advanced diagnostic techniques, including metagenomic next-generation sequencing, but there are also known pathogens which have expanded their geographic distribution to infect non-immune individuals. Factors including population growth, climate change, the increase in animal and human interface, and an increase in international travel and trade are contributing to the expansion of emerging and re-emerging pathogens. Challenges exist around antimicrobial misuse giving rise to antimicrobial-resistant infectious neurotropic organisms and increased susceptibility to infection related to the expanded use of immunomodulatory treatments. In this article, we will review key concepts around emerging and re-emerging pathogens and discuss factors associated with neurotropism and neuroinvasion. We highlight several neurotropic pathogens of interest, including West Nile virus (WNV), Zika Virus, Japanese Encephalitis Virus (JEV), and Tick-Borne Encephalitis Virus (TBEV). We emphasize neuroinfectious diseases which impact the central nervous system (CNS) and focus on flaviviruses, a group of vector-borne pathogens that have expanded globally in recent years and have proven capable of widespread outbreak.

## Predation risk effects on larval development and adult life of *Aedes aegypti* mosquito.

**Cozzer, G., Rezende, R., Lara, T., Machado, G., Dal Magro, J., Albeny-Simões, D.**
20-06-2022
*Bull Entomol Res*
https://doi.org/10.1017/S000748532200027X

Biological control is one of the methods available for control of *Aedes aegypti* populations. We used experimental microcosms to evaluate the effects of actual predation and

predation risk by dragonfly larvae (Odonata) on larval development, adult longevity, and adult size of *Ae. aegypti*. We used six treatments: control, removal, variable density cues (Cues VD), fixed density cues (Cues FD), variable density predator (Predator VD), and fixed density predator (Predator FD) ($n$ = 5 each). Predator treatments received one dragonfly larva. Cue treatments were composed of crushed *Ae. aegypti* larvae released into the microcosm. For the FD treatments, we maintained a larval density of 200 individuals. The average mortality of *Ae. aegypti* larvae in the Predator VD treatment was used as the standard mortality for the other treatments. Mosquitoes from the Predator VD and Cues VD treatments developed faster, and adults were larger and had greater longevity compared to all other treatments, likely due to the higher food availability from larval density reduction. High larval density negatively affected larval developmental time, adult size, and longevity. Males were less sensitive to density-dependent effects. Results from this study suggest that the presence of predators may lead to the emergence of adult mosquitoes with greater fitness, causing an overall positive effect on *Ae. aegypti* population growth rates.

## Clinical evaluation of the BioFire Global Fever Panel for the identification of malaria, leptospirosis, chikungunya, and dengue from whole blood: a prospective, multicentre, cross-sectional diagnostic accuracy study.

**Manabe, Y., Betz, J., Jackson, O., Asoala, V., Bazan, I., Blair, P., Chang, A., Chusri, S., Crump, J., Edgel, K., Faix, D., Fernandez, S., Fox, A., Garcia, J., Grogl, M., Hansen, E., Heang, V., House, S., Jongsakul, K., Kaburise, M., Klungthong, C., Lamorde, M., Letizia, A., Lorenzana, I., Luy, M., Maro, V., Mores, C., Myers, C., Oduro, A., Parham, L., Porzucek, A., Prouty, M., Rabiger, D., Rubach, M., Siles, C., Silva, M., Ukachu, C., Waitumbi, J., Phillips, C., Jones, B.**
15-06-2022
*Lancet Infect Dis*
https://pubmed.ncbi.nlm.nih.gov/35716700

Background: Acute febrile illness is a common presentation for patients at hospitals globally. Assays that can diagnose a variety of common pathogens in blood could help to establish a diagnosis for targeted disease management. We aimed to evaluate the performance of the BioFire Global Fever Panel (GF Panel), a multiplex nucleic acid amplification test performed on whole blood specimens run on the BioFire FilmArray System, in the diagnosis of several pathogens that cause acute febrile illness. Methods: We did a prospective, multicentre, cross-sectional diagnostic accuracy study to evaluate the GF Panel. Consenting adults and children older than 6 months presenting with fever in the previous 2 days were enrolled consecutively in sub-Saharan Africa (Ghana, Kenya, Tanzania, Uganda), southeast Asia (Cambodia, Thailand), central and South America (Honduras, Peru), and the USA (Washington, DC; St Louis, MO). We assessed the performance of six analytes (chikungunya virus, dengue virus [serotypes 1-4], Leptospira spp, Plasmodium spp, Plasmodium falciparum, and Plasmodium vivax or Plasmodium ovale) on the GF Panel. The performance of the GF Panel was assessed using comparator PCR assays with different primers followed by bidirectional sequencing on nucleic acid extracts from the same specimen. We calculated the positive percent agreement and negative percent agreement of the GF Panel with respect to the comparator assays. This study is registered with ClinicalTrials.gov, NCT02968355. Findings: From March 26, 2018, to Sept 30, 2019, 1965 participants were enrolled at ten sites worldwide. Of the 1875 participants with analysable results, 980 (52·3%) were female and the median age was 22 years (range 0-100). At least one analyte was detected in 657 (35·0%) of 1875 specimens. The GF Panel had a positive percent agreement for the six analytes evaluated as follows: chikungunya virus 100% (95% CI 86·3-100), dengue virus 94·0% (90·6-96·5), Leptospira spp 93·8% (69·8-99·8), Plasmodium spp 98·3% (96·3-99·4), P falciparum 92·7% (88·8-95·6), and P vivax or P ovale 92·7% (86·7-96·6). The GF Panel had a negative percent agreement equal to or greater than 99·2% (98·6-99·6) for all analytes. Interpretation: This 1 h sample-to-answer, molecular device can detect common causative agents of acute febrile illness with excellent positive percent agreement and negative percent agreement directly in whole blood. The targets of the assay are prevalent in tropical and subtropical regions globally, and the assay could help to provide both public health surveillance and individual diagnoses. Funding: BioFire Defense, Joint Project Manager for Medical Countermeasure Systems and US Army Medical Materiel Development Activity, and National Institute of Allergy and Infectious Diseases.

## Growth hormone attenuates the brain damage caused by ZIKV infection in mice.

**Zhen, Z., Wu, N., Fan, D., Ai, J., Song, Z., Chang, J., Wang, P., Wu, Y., An, J.**
14-06-2022
*Virol Sin*
https://pubmed.ncbi.nlm.nih.gov/35714850

As a member of vector-borne viruses, Zika virus (ZIKV) can cause microcephaly and various neurological symptoms in newborns. Previously, we found that ZIKV could infect hypothalamus, causing a decrease in growth hormone (GH) secretion, growth delay and deficits in learning and memory in suckling mice. Early administration of GH can improve the cognitive function of the mice. Therefore, in this study we further investigated the mechanism underlying the protective role of GH in ZIKV infection in suckling mice. Our results showed that GH could effectively reduce brain damage caused by ZIKV infection via reducing cell apoptosis and inflammatory response rather than inhibiting viral replication. Our results provide important evidences not only for understanding the mechanism underlying ZIKV-associated neurological symptoms but also for the treatment of ZIKV infection.

## Adenovirus vector-based vaccines as forefront approaches in fighting the battle against flaviviruses.

**Shoushtari, M., Roohvand, F., Salehi-Vaziri, M., Arashkia, A., Bakhshi, H., Azadmanesh, K.**
17-06-2022
*Hum Vaccin Immunother*
https://doi.org/10.1080/21645515.2022.2079323

Flaviviruses are arthropod-borne viruses (arboviruses) that have been recently considered among the significant public health problems in defined geographical regions. In this line, there have been vaccines approved for some flaviviruses including dengue virus (DENV), Japanese encephalitis virus (JEV), yellow fever virus (YFV), and tick-borne encephalitis virus (TBEV), although the efficiency of such vaccines thought to be questionable. Surprisingly, there are no effective vaccine for many other hazardous flaviviruses, including West Nile and Zika viruses. Furthermore, in spite of approved vaccines for some flaviviruses, for example DENV, alternative prophylactic vaccines seem to be still needed for the protection of a broader population, and it originates from the unsatisfying safety, and the efficacy of vaccines that have been introduced. Thus, adenovirus vector-based vaccine candidates are suggested to be effective, safe, and reliable. Interestingly, recent widespread use of adenovirus vector-based vaccines for the COVID-19 pandemic have highlighted the importance and feasibility of their widespread application. In this review, the applicability of adenovirus vector-based vaccines, as promising approaches to harness the diseases caused by Flaviviruses, is discussed.

## Socioeconomic disparities associated with symptomatic Zika virus infections in pregnancy and congenital microcephaly: A spatiotemporal analysis from Goiânia, Brazil (2016 to 2020).

**Rosado, L., Aquino, E., Brickley, E., França, D., Silva, F., Silva, V., Lopes, A., Turchi, M.**
17-06-2022
*PLoS Negl Trop Dis*
https://doi.org/10.1371/journal.pntd.0010457

The Zika virus (ZIKV) epidemic, which was followed by an unprecedented outbreak of congenital microcephaly, emerged in Brazil unevenly, with apparent pockets of susceptibility. The present study aimed to detect high-risk areas for ZIKV infection and microcephaly in Goiania, a large city of 1.5 million inhabitants in Central-West Brazil. Using geocoded surveillance data from the Brazilian Information System for Notifiable Diseases (SINAN) and from the Public Health Event Registry (RESP-microcefalia), we analyzed the spatiotemporal distribution and socioeconomic indicators of laboratory confirmed (RT-PCR and/or anti-ZIKV IgM ELISA) symptomatic ZIKV infections among pregnant women and clinically confirmed microcephaly in neonates, from 2016 to 2020. We investigated temporal patterns by estimating the risk of symptomatic maternal ZIKV infections and microcephaly per 1000 live births per month. We examined the spatial distribution of maternal ZIKV infections and microcephaly cases across the 63 subdistricts of Goiania by manually plotting the geographical coordinates. We used spatial scan statistics estimated by discrete Poisson models to detect high clusters of maternal ZIKV infection and microcephaly and compared the distributions by socioeconomic indicators measured at the subdistrict level. In total, 382 lab-confirmed cases of maternal ZIKV infections, and 31 cases of microcephaly were registered in the city of Goiania. More than 90% of maternal cases were reported between 2016 and 2017. The highest incidence of ZIKV cases among pregnant women occurred between February and April 2016. A similar pattern was observed in the following year, although with a lower number of cases, indicating seasonality for ZIKV infection, during the local rainy season. Most congenital microcephaly cases occurred with a time-lag of 6 to 7 months after the peak of maternal ZIKV infection. The highest estimated incidence of maternal ZIKV infections and microcephaly were 39.3 and 2.5 cases per 1000 livebirths, respectively. Districts with better socioeconomic indicators and with higher proportions of self-identified white inhabitants were associated with lower risks of maternal ZIKV infection. Overall, the findings indicate heterogeneity in the spatiotemporal patterns of maternal ZIKV infections and microcephaly, which were correlated with seasonality and included a high-risk geographic cluster. Our findings identified geographically and socio-economically underprivileged groups that would benefit from targeted interventions to reduce exposure to vector-borne infections.

## Seroepidemiological reconstruction of long-term chikungunya virus circulation in Burkina Faso and Gabon.

**Kyungah Lim, J., Ridde, V., Todagbe Agnandji, S., Lell, B., Yaro, S., Seung Yang, J., Hoinard, D., Weaver, S., Vanhomwegen, J., Salje, H., Yoon, I.**
17-06-2022
*J Infect Dis*
https://pubmed.ncbi.nlm.nih.gov/35710849

Chikungunya virus (CHIKV) is a major public health concern worldwide. However, infection levels are rarely known, especially in Africa. We recruited individuals from Ouagadougou, Burkina Faso and Lambaréné, Gabon (age range: 1-55), tested their blood for CHIKV antibodies and used serocatalytic models to reconstruct epidemiological histories. In Ouagadougou, 291/999 (29.1%) individuals were seropositive, ranging from 2% among those <10y to 66% in those 40-55y. We estimated there were 7 outbreaks since the 1970s but none since 2001 resulting in 600,000 infections in the city, none of which were reported. However, we could not definitively conclude whether infections were due to CHIKV or o'nyong-nyong, another alphavirus. In Lambaréné, 117/427 (27%) participants were seropositive. Our model identified a single outbreak sometime since 2007, consistent with the only reported CHIKV outbreak in the country. These findings suggest sporadic outbreaks in these settings and that the burden remains undetected or incorrectly attributed.

## A gossypol derivative effectively protects against Zika and dengue virus infection without toxicity.

**Gao, Y., Tai, W., Wang, X., Jiang, S., Debnath, A., Du, L., Chen, S.**
15-06-2022
*BMC Biol*
https://doi.org/10.1186/s12915-022-01344-w

**Background:** Zika virus (ZIKV) and dengue virus (DENV) cause microcephaly and dengue hemorrhagic fever, respectively, leading to severe problems. No effective antiviral agents are approved against infections of these flaviviruses, calling for the need to develop potent therapeutics. We previously identified gossypol as an effective inhibitor against ZIKV and DENV infections, but this compound is toxic and not suitable for in vivo treatment. **Results:** In this study, we showed that gossypol derivative ST087010 exhibited potent and broad-spectrum in vitro inhibitory activity against infections of at least ten ZIKV strains isolated from different hosts, time periods, and countries, as well as DENV-1-4 serotypes, and significantly reduced cytotoxicity compared to gossypol. It presented broad-spectrum in vivo protective efficacy, protecting ZIKV-infected Ifnar1$^{-/-}$ mice from lethal challenge, with increased survival and reduced weight loss. Ifnar1$^{-/-}$ mice treated with this gossypol derivative decreased viral titers in various tissues, including the brain and testis, after infection with ZIKV at different human isolates. Moreover, ST087010 potently blocked ZIKV vertical transmission in pregnant Ifnar1$^{-/-}$ mice, preventing ZIKV-caused fetal death, and it was safe for pregnant mice and their pups. It also protected DENV-2-challenged Ifnar1$^{-/-}$ mice against viral replication by reducing the viral titers in the brain, kidney, heart, and sera. **Conclusions:** Overall, our data indicate the potential for further development of this gossypol derivative as an effective and safe broad-spectrum therapeutic agent to treat ZIKV and DENV diseases.

## Novel chikungunya vaccine shows promise for durable protection.

**Stephenson, K.**
13-06-2022
*Lancet Infect Dis*
https://pubmed.ncbi.nlm.nih.gov/35709799

## Safety and immunogenicity of PXVX0317, an aluminium hydroxide-adjuvanted chikungunya virus-like particle vaccine: a randomised, double-blind, parallel-group, phase 2 trial.

**Bennett, S., McCarty, J., Ramanathan, R., Mendy, J., Richardson, J., Smith, J., Alexander, J., Ledgerwood, J., de Lame, P., Royalty Tredo, S., Warfield, K., Bedell, L.**
13-06-2022
*Lancet Infect Dis*
https://pubmed.ncbi.nlm.nih.gov/35709798

**Background:** Chikungunya virus (CHIKV) disease is an ongoing public health threat. We aimed to evaluate the safety and immunogenicity of PXVX0317, an aluminium hydroxide-adjuvanted formulation of a CHIKV virus-like particle (VLP) vaccine. **Methods:** This randomised, double-blind, parallel-group, phase 2 trial was conducted at three clinical trial centres in the USA. Eligible participants were healthy CHIKV-naïve adults aged 18-45 years. Participants were stratified by site and randomly assigned (1:1:1:1:1:1:1:1) to one of the eight vaccination groups using a block size of 16. Group 1 received two doses of unadjuvanted PXVX0317 28 days apart (2 × 20 μg; standard); all other groups received adjuvanted PXVX0317: groups 2-4 received two doses 28 days apart (2 × 6 μg [group 2], 2 × 10 μg [group 3], or 2 × 20 μg [group 4]; standard); group 4 also received a booster dose 18 months after the first active injection (40 μg; standard plus booster); groups 5-7 received two doses 14 days apart (2 × 6 μg [group 5], 2 × 10 μg [group 6], or 2 × 20 μg [group 7]; accelerated); and group 8 received one dose (1 × 40 μg; single). The primary endpoint was the geometric mean titre of anti-CHIKV neutralising antibody on day 57 (28 days after the last vaccination), assessed in the immunogenicity-evaluable population. Additionally, we assessed safety. This trial is registered at ClinicalTrials.gov, NCT03483961. **Findings:** This trial was conducted from April 18, 2018, to Sept 21, 2020; 468 participants were assessed for eligibility. Of these, 415 participants were randomly assigned to eight groups (n=53 in groups 1, 5, and 6; n=52 in groups 2 and 8; n=51 in groups 3 and 7; and n=50 in group 4) and 373 were evaluable for immunogenicity. On day 57, serum neutralising antibody geometric mean titres were 2057·0 (95% CI 1584·8-2670·0) in group 1, 1116·2 (852·5-1461·4; p=0·0015 vs group 1 used as a reference) in group 2, 1465·3 (1119·1-1918·4; p=0·076) in group 3, 2023·8 (1550·5-2641·7; p=0·93) in group 4, 920·1 (710·9-1190·9; p<0·0001) in group 5, 1206·9 (932·4-1562·2; p=0·0045) in group 6, 1562·8 (1204·1-2028·3; p=0·14) in group 7, and 1712·5 (1330·0-2205·0; p=0·32) in group 8. In group 4, a booster dose increased serum neutralising antibody geometric mean titres from 215·7 (95% CI 160·9-289·1) on day 547 to 10 941·1 (7378·0-16 225·1) on day 575. Durability of the immune response (evaluated in groups 1, 4, and 8) was shown up to 2 years. The most common solicited adverse event was pain at the injection site, reported in 12 (23%) of 53 participants who received the unadjuvanted vaccine (group 1) and 111 (31%) of 356 who received the adjuvanted vaccine. No vaccine-related serious adverse events were reported. **Interpretation:** PXVX0317 was well tolerated and induced a robust and durable serum neutralising antibody immune response against CHIKV up to 2 years. A single 40 μg injection of adjuvanted PXVX0317 is being further investigated in phase 3 clinical trials (NCT05072080 and NCT05349617). **Funding:** Emergent BioSolutions.

## The expression of circulating hsa-miR-126-3p in dengue-infected Thai pediatric patients.

**Sriprapun, M., Rattanamahaphoom, J., Sriburin, P., Chatchen, S., Limkittikul, K., Sirivichayakul, C.**
16-06-2022
*Pathog Glob Health*
https://doi.org/10.1080/20477724.2022.2088465

Circulating hsa-miRNA-126 (CmiR-126) has been reported to involve in the pathogenesis of many infectious diseases including dengue virus infection. However, no prior study has been conducted to describe more details in dengue-infected pediatric patients. This study aimed to describe CmiR-126-3p in dengue-infected pediatric patients during the febrile and convalescent phases. Additionally, the correlations between CmiR-126-3p and other relevant clinical laboratory factors were investigated. Sixty paired-serum specimens collected during febrile and convalescent phases were retrieved from patients with dengue fever (DF) (n = 30) and dengue hemorrhagic fever (DHF) (n = 30). Thirty paired-serum specimens collected from non-dengue acute febrile illness patients (AFI) were included as the control group. CmiR-126-3p was determined using reverse transcription quantitative real-time polymerase-chain reaction (RT-qPCR). Relative miRNA expression was calculated as $2^{-\Delta Ct}$ using CmiR-16-5p for data normalization. CmiR-126-3p expression during febrile and convalescent phases in dengue-infected patients was significantly lower than AFI ($p < 0.05$). However, miRNA levels were not different ($p > 0.05$) compared between DF and DHF and between primary and secondary infection. CmiR-126-3p levels in DF in the convalescent were significantly higher than in the febrile phase ($p = 0.025$). No association between CmiR-126-3p and hematocrit, WBC level, platelet count, WBC differential count or dengue viral load was observed ($p > 0.05$). The data suggest that hsa-miR-126-3p involved in pathogenesis of dengue infection and may be a promising early and late biomarker for DENV infection. However, hsa-miR-126-3p alone cannot be used as a predictor for dengue severity.

## Preparation and application of chikungunya pseudovirus containing double reporter genes.

**Su, C., Ding, K., Xu, J., Wu, J., Liu, J., Shen, J., Zhou, H., Liu, H.**
14-06-2022
*Sci Rep*
https://doi.org/10.1038/s41598-022-13230-0

Chikungunya virus (CHIKV), a highly infectious and rapidly spread viral pathogen, is classified as a pathogenic agent at the biosafety level 3. Operation of live authentic CHIKV needs a specific laboratory with the P3 or above containment, which greatly confines the CHIKV-associated studies. To establish an evaluation system of CHIKV that can be utilized in a BSL2 laboratory, we constructed a pseudovirus (PsV) system of CHIKV containing double reporter genes (ZsGreen1 and luciferase). The fluorescent ZsGreen1 is a convenient and cheap reporter for monitoring the efficiency of transfection and titration of PsV. The enzyme luciferase is a sensitive reporter for the application of PsV to neutralization assay or drug screening. The CHIKV PsV produced in this study, with a titer of up to $3.16\times10^6$ TU/ml, was confirmed by Western blotting and transmission electronic microscopy (TEM). Finally, we developed a microneutralization assay with the CHIKV PsV produced in this study, which was successfully applied to evaluate neutralizing activities of convalescent sera from CHIKV-infected patients. In summary, we have established a convenient and sensitive double-reporter CHIKV pseudovirus system, which provides a safe and effective platform for screening anti-CHIKV drugs and evaluating vaccines against CHIKV.

## Disruption of spatiotemporal clustering in dengue cases by wMel Wolbachia in Yogyakarta, Indonesia.

**Dufault, S., Tanamas, S., Indriani, C., Utarini, A., Ahmad, R., Jewell, N., Simmons, C., Anders, K.**
14-06-2022
*Sci Rep*
https://doi.org/10.1038/s41598-022-13749-2

Dengue exhibits focal clustering in households and neighborhoods, driven by local mosquito population dynamics, human population immunity, and fine scale human and mosquito movement. We tested the hypothesis that spatiotemporal clustering of homotypic dengue cases is disrupted by introduction of the arbovirus-blocking bacterium Wolbachia (wMel-strain) into the Aedes aegypti mosquito population. We analysed 318 serotyped and geolocated dengue cases (and 5921 test-negative controls) from a randomized controlled trial in Yogyakarta, Indonesia of wMel deployments. We find evidence of spatial clustering up to 300 m among the 265 dengue cases (3083 controls) in the untreated trial arm. Participant pairs enrolled within 30 days and 50 m had a 4.7-fold increase (compared to 95% CI on permutation-based null distribution: 0.1, 1.2) in the odds of being homotypic (i.e. potentially transmission-related) as compared to pairs occurring at any distance. In contrast, we find no evidence of spatiotemporal clustering among the 53 dengue cases (2838 controls) resident in the wMel-treated arm. Introgression of wMel Wolbachia into Aedes aegypti mosquito populations interrupts focal dengue virus transmission leading to reduced case incidence; the true intervention effect may be greater than the 77% efficacy measured in the primary analysis of the Yogyakarta trial.

## Climate variability and Aedes vector indices in the southern Philippines: An empirical analysis.

**Murphy, A., Salazar, F., Bonsato, R., Uy, G., Ebol, A., Boholst, R., Davis, C., Frentiu, F., Bambrick, H., Devine, G., Hu, W.**
14-06-2022
*PLoS Negl Trop Dis*
https://doi.org/10.1371/journal.pntd.0010478

Background: Vector surveillance is an essential public health tool to aid in the prediction and prevention of mosquito borne diseases. This study compared spatial and temporal trends of vector surveillance indices for Aedes vectors in the southern Philippines, and assessed potential links between vector indices and climate factors. Methods: We analysed routinely collected larval and pupal surveillance data from residential areas of 14 cities and 51 municipalities during 2013-2018 (House, Container, Breteau and Pupal Indices), and used linear regression to explore potential relationships between vector indices and climate variables (minimum temperature,

maximum temperature and precipitation). **Results:** We found substantial spatial and temporal variation in monthly Aedes vector indices between cities during the study period, and no seasonal trend apparent. The House (HI), Container (CI) and Breteau (BI) Indices remained at comparable levels across most surveys (mean HI = 15, mean CI = 16, mean BI = 24), while the Pupal Productivity Index (PPI) was relatively lower in most months (usually below 5) except for two main peak periods (mean = 49 overall). A small proportion of locations recorded high values across all entomological indices in multiple surveys. Each of the vector indices were significantly correlated with one or more climate variables when matched to data from the same month or the previous 1 or 2 months, although the effect sizes were small. Significant associations were identified between minimum temperature and HI, CI and BI in the same month (R2 = 0.038, p = 0.007; R2 = 0.029, p = 0.018; and R2 = 0.034, p = 0.011, respectively), maximum temperature and PPI with a 2-month lag (R2 = 0.031, p = 0.032), and precipitation and HI in the same month (R2 = 0.023, p = 0.04). **Conclusions:** Our findings indicated that larval and pupal surveillance indices were highly variable, were regularly above the threshold for triggering vector control responses, and that vector indices based on household surveys were weakly yet significantly correlated with city-level climate variables. We suggest that more detailed spatial and temporal analyses of entomological, climate, socio-environmental and Aedes-borne disease incidence data are necessary to ascertain the most effective use of entomological indices in guiding vector control responses, and reduction of human disease risk.

## Effectiveness of CHIKV vaccine VLA1553 demonstrated by passive transfer of human sera.

**Roques, P., Fritzer, A., Dereuddre-Bosquet, N., Wressnigg, N., Hochreiter, R., Bossevot, L., Pascal, Q., Guehenneux, F., Bitzer, A., Corbic Ramljak, I., Le Grand, R., Lundberg, U., Meinke, A.**

14-06-2022

*JCI Insight*

https://doi.org/10.1172/jci.insight.160173

Chikungunya virus (CHIKV) is a re-emerging mosquito-borne alphavirus responsible for numerous outbreaks. Chikungunya can cause debilitating acute and chronic disease. Thus, the development of a safe and effective CHIKV vaccine is an urgent global health priority.This study evaluated the effectiveness of the live-attenuated CHIKV vaccine VLA1553 against WT CHIKV infection by using passive transfer of sera from vaccinated volunteers to non-human primates (NHP) subsequently exposed to WT CHIKV and established a serological surrogate of protection. We demonstrated that human VLA1553 sera transferred to NHPs conferred complete protection from CHIKV viremia and fever after challenge with homologous WT CHIKV. In addition, serum transfer protected animals from other CHIKV associated clinical symptoms and from CHIKV persistence in tissue. Based on this passive transfer study, a 50% micro plaque reduction neutralization test titer of ≥150 was determined as a surrogate of protection which was supported by analysis of samples from a sero-epidemiological study.In conclusion, considering the unfeasibility of an efficacy trial due to the unpredictability and explosive, rapidly moving nature of chikungunya outbreaks, the definition of a surrogate of protection for VLA1553 is an important step towards vaccine licensure to reduce the medical burden caused by chikungunya.

## Olfactory outcomes in Zika virus-associated Guillain-Barré syndrome.

**Lazarini, F., Lannuzel, A., Cabié, A., Michel, V., Madec, Y., Chaumont, H., Calmont, I., Favrat, M., ZikaSmell Working Group, Lazarini, F., Lannuzel, A., Cabié, A., Calmont, I., Abel, S., Cabras, O., Marquise, A., Pircher, M., Signate, A., Celeste, C., Chaumont, H., Lackmy, A., Lepage, G., Lobjois, Q., Petit, A., Tressières, B., Teissier, N., Roze, E., Buivan, T., Conquet, L., Laude, H., Lledo, P., Madec, Y., Mottez, E., Taieb, F., Ungeheuer, M., Montagutelli, X., Roze, E., Lledo, P.**

14-06-2022

*Eur J Neurol*

https://doi.org/10.1111/ene.15444

**Background:** Zika Virus (ZIKV) infection has been associated with Guillain-Barré Syndrome (GBS). Yet, little is known about the consequence of ZIKV infection on olfaction in humans. **Methods:** Just right before the COVID-19 outbreak, we prospectively investigated the olfactory capacities of 19 patients with ZIKV-associated GBS from the French West Indies and compared them to 9 controls from the same population, with a GBS of similar severity but independent of Zika infection. To provide further evidence that ZIKV infection induces smell alteration, we investigated the consequences of ZIKV infection on olfactory abilities using a mouse model. **Results:** Patients with GBS-Zika+ had a poorer olfactory function than GBS-non-Zika, even one to two years after the acute phase. The proportion of patients with hyposmia was significantly higher in GBS-Zika+ than in GBS-non-Zika group (68.4% versus 22.2%, P=0.042). These deficits were characterized by lower threshold and identification scores and were independent from GBS severity. Additionally, ZIKV infection was found to impair olfaction in immunodeficient mice infected with ZIKV. High viral load was observed in their olfactory system and downstream brain structures. ZIKV promoted both cellular damages in the olfactory neuroepithelium and protracted inflammation of the olfactory bulb, likely accounting for smell alteration. **Conclusions:** Patients with ZIKV-related GBS had a poorer long-term olfactory function than patients with GBS-non-Zika and ZIKV-infected mice are hyposmic. These observations suggest that ZIKV belongs to the list of viruses affecting the olfactory system. Clinical evaluation of the olfactory system should be considered for ZIKV-infected patients.

## A taRNA vaccine candidate induces a specific immune response that protects mice against Chikungunya virus infections.

**Schmidt, C., Haefner, E., Gerbeth, J., Beissert, T., Sahin, U., Perkovic, M., Schnierle, B.**

02-05-2022
*Mol Ther Nucleic Acids*
https://doi.org/10.1016/j.omtn.2022.04.036

The arthritogenic alphavirus, chikungunya virus (CHIKV), is now present in almost 100 countries worldwide. Further spread is very likely, which raises public health concerns. CHIKV infections cause fever and arthralgia, which can be debilitating and last for years. Here, we describe a CHIKV vaccine candidate based on *trans*-amplifying RNA (taRNA). The vaccine candidate consists of two RNAs: a non-replicating mRNA encoding for the CHIKV nonstructural proteins, forming the replicase complex and a *trans*-replicon (TR) RNA encoding the CHIKV envelope proteins. The TR-RNA can be amplified by the replicase in *trans*, and small RNA amounts can induce a potent immune response. The TR-RNA was efficiently amplified by the CHIKV replicase *in vitro*, leading to high protein expression, comparable to that generated by a CHIKV infection. In addition, the taRNA system did not recombine to replication-competent CHIKV. Using a prime-boost schedule, the vaccine candidate induced potent CHIKV-specific humoral and cellular immune responses *in vivo* in a mouse model. Notably, mice were protected against a high-dose CHIKV challenge infection with two vaccine doses of only 1.5 µg RNA. Therefore, taRNAs are a promising safe and efficient vaccination strategy against CHIKV infections.

### Contrasting behavior between the three human monocyte subsets in dengue pathophysiology.

**Maheshwari, D., Saini, K., Singh, P., Singla, M., Nayak, K., Aggarwal, C., Chawla, Y., Bajpai, P., Kaur, M., Gunisetty, S., Eberhardt, C., Nyodu, R., Moore, K., Suthar, M., Medigeshi, G., Anderson, E., Lodha, R., Kabra, S., Ahmed, R., Chandele, A., Murali-Krishna, K.**
10-05-2022
*iScience*
https://doi.org/10.1016/j.isci.2022.104384

Monocytes are known to play a critical role in dengue pathophysiology. However, which monocyte subset expresses what inflammatory mediator(s) and what transcriptional features distinguish each of the monocyte subset *in vivo* remain poorly understood. In this study we provide a detailed transcriptional analysis of the three human monocyte subsets in healthy children and in children with dengue febrile illness. Notably, we found that the $CD14^{+}$ CD16high intermediate monocyte subset from dengue patients highly upregulated key genes involved in mediating inflammation, endothelial dysfunction, vascular permeability, tissue extravasation, and clot prevention compared to healthy children. The $CD14^{+}$CD16low classical monocytes shared some of these features. These two subsets increased massively in patients with severe dengue. By contrast, the $CD14^{-}$CD16high nonclassical monocyte subset upregulated key genes involved in vasoconstriction, endothelial barrier stability, and are involved in endothelial patrolling while showing a significant decline from circulation. These findings improve our understanding of monocyte responses in dengue.

### A protocol to assess cellular bioenergetics in flavivirus-infected cells.

**Low, J., Yau, C., Zhang, S., Tan, H., Ooi, E., Chan, K.**
11-04-2022
*STAR Protoc*
https://doi.org/10.1016/j.xpro.2022.101297

Aberrant cellular bioenergetics has detrimental consequences in host cells. For instance, pathogenic Zika virus strains can suppress mitochondria respiration and glycolytic functions, disrupting cellular bioenergetics that leads to apoptosis. Herein, we describe methods for flavivirus propagation, titering and infection, cell preparation, and procedures for mitochondrial and glycolytic stress tests. The protocol enables assessment of cellular respiration and glycolytic flux in flavivirus-infected cells. For complete details on the use and execution of this protocol, please refer to Yau et al. (2021).

## RAGE

### Development of an efficient veterinary rabies vaccine production process in the avian suspension cell line AGE1.CR.pIX.

**Trabelsi, K., Zakour, M., Jordan, I., Sandig, V., Rourou, S., Kallel, H.**
17-06-2022
*BMC Biotechnol*
https://doi.org/10.1186/s12896-022-00747-5

Background: Mass vaccination of dogs as important rabies reservoir is proposed to most effectively reduce and eliminate rabies also in humans. However, a minimum coverage of 70% needs to be achieved for control of the disease in zoonotic regions. In numerous developing countries, dog vaccination rate is still dangerously low because of economic constraints and due to a high turnover in dog populations. Improved vaccine production processes may help to alleviate cost and supply limitations. In this work, we studied and optimized the replication and vaccine potency of PV rabies virus strain in the muscovy-duck derived AGE1.CR and AGE1.CR.pIX suspension cell lines. Results: The BHK-21-adapted PV rabies virus strain replicated efficiently in the avian cell lines without requirement for prior passaging. CR.pIX was previously shown to augment heat shock responses and supported slightly higher infectious titers compared to the parental CR cell line. Both cell lines allowed replication of rabies virus also in absence of recombinant IGF, the only complex component of the chemically defined medium that was developed for the two cell lines. After scale-up from optimization experiments in shake flask to production in 7-l bioreactors peak virus titers of $2.4\times10^{8}$ FFU/ml were obtained. The potency of inactivated rabies virus harvest according to the NIH test was 3.5 IU/ml. Perfusion with the chemically defined medium during the virus replication phase improved the potency of the vaccine twofold, and increased the number of doses 9.6 fold.

Conclusion: This study demonstrates that a rabies vaccine for animal vaccination can be produced efficiently in the AGE1.CR.pIX suspension cell line in a scalable process in chemically defined medium.

### Structure of the rabies virus glycoprotein trimer bound to a prefusion-specific neutralizing antibody.

**Callaway, H., Zyla, D., Larrous, F., de Melo, G., Hastie, K., Avalos, R., Agarwal, A., Corti, D., Bourhy, H., Saphire, E.**
17-06-2022
*Sci Adv*
https://doi.org/10.1126/sciadv.abp9151

Rabies infection is nearly 100% lethal if untreated and kills more than 50,000 people annually, many of them children. Existing rabies vaccines target the rabies virus glycoprotein (RABV-G) but generate short-lived immune responses, likely because the protein is heterogeneous under physiological conditions. Here, we report the 3.39 Å cryo-electron microscopy structure of trimeric, prefusion RABV-G complexed with RVA122, a potently neutralizing human antibody. RVA122 binds to a quaternary epitope at the top of RABV-G, bridging domains and stabilizing RABV-G protomers in a prefusion state. RABV-G trimerization involves side-to-side interactions between the central α helix and adjacent loops, rather than contacts between central helices, and interactions among the fusion loops at the glycoprotein base. These results provide a basis from which to develop improved rabies vaccines based on RABV-G stabilized in the prefusion conformation.

### Optimization of BRET saturation assays for robust and sensitive cytosolic protein-protein interaction studies.

**Besson, B., Eun, H., Kim, S., Windisch, M., Bourhy, H., Grailhe, R.**
15-06-2022
*Sci Rep*
https://doi.org/10.1038/s41598-022-12851-9

Bioluminescence resonance energy transfer (BRET) saturation is a method of studying protein-protein interaction (PPI) upon quantification of the dependence of the BRET signal on the acceptor/donor (A:D) expression ratio. In this study, using the very bright Nluc/YFP BRET pair acquired respectively with microplate reader and automated confocal microscopy, we significantly improved BRET saturation assay by extending A:D expression detection range and normalizing A:D expression with a new BRET-free probe. We next found that upon using variable instead of fixed amount of donor molecules co-expressed with increasing acceptor concentrations, BRET saturation assay robustness can be further improved when studying cytosolic protein, although the relative amounts of dimers (BRETmax) and the relative dimer affinity (BRET50) remain similar. Altogether, we show that our method can be applied to many PPI networks, involving the NF-κB pathway, high-affinity nanobody, rabies virus-host interactions, mTOR complex and JAK/STAT signaling. Altogether our approach paves the way for robust PPI validation and characterization in living cells.

## TRACHOME

### Prevalence of active trachoma and its associated factors among 1-9 years of age children from model and non-model kebeles in Dangila district, northwest Ethiopia.

**Genet, A., Dagnew, Z., Melkie, G., Keleb, A., Motbainor, A., Mebrat, A., Leshargie, C.**
15-06-2022
*PLoS One*
https://doi.org/10.1371/journal.pone.0268441

Background: Trachoma is the leading infectious disease that leads to blindness worldwide, especially in developing countries. Though Ethiopia had targeted a trachoma elimination program by 2020, the problem worsens, particularly in the Amhara Region. Even though sustained intervention measures are undertaken across the region, it is unclear why trachoma is still a significant public health problem. So, this study assessed the prevalence of active trachoma and associated factors among 1-9 years of age children from model and non-model kebeles in Dangila district Amhara Region, Northwest Ethiopia. Methods: A community-based comparative cross-sectional study was conducted from 20th September 2019 to 29th October 2019. A multistage stratified random sampling technique was used to reach 704 children from model and non-model kebeles. Samples were allocated proportionally to model and non-model kebeles. A structured and pretested data collection tool and observational checklist was used to manage the necessary data. Data were coded and entered in Epidata version 4.6, and further analysis was done using SPSS version 20 software. Bivariable and multivariable logistic regression analysis was employed to identify factors associated with active trachoma. Adjusted Odds Ratios (AOR), p-value, and respected Confidence Interval (CI) were used to report the findings. Results: Seven hundred four children were included in this study, with a response rate of 97.8%. The overall prevalence of active trachoma was 6% (95% CI: 4.5, 8.1). The prevalence of active trachoma among non-model and model Kebele was not significantly different. Still, the prevalence of active trachoma among children from model Kebele were [4.5%, (95% CI: 2.4%, 7.1%)] relatively lower compared with non-model kebeles, [7.6%, 95% CI: (4.9%, 10.9%)]. Moreover, not using latrine (AOR = 4.29, 95% CI: 1.96, 9.34), fly-eye contact (AOR = 2.59, 95% CI: 1.11, 6.03), presence of sleep in eyes (AOR = 2.46, 95% CI: 1.10, 5.47), presence of ocular discharge (AOR = 2.79, 95% CI: 1.30, 6.00), presence of nasal discharges (AOR = 2.67, 95% CI: 1.21, 5.90) and washing faces with soap (AOR = 0.22, 95% CI: 0.07, 0.69) were found significantly associated with the prevalence of active trachoma among

children 1-9 years old. **Conclusions:** The prevalence of active trachoma in the model and non-model kebeles was high and did not show a statistical difference. Attention to be given to latrine utilization, washing face with soap, and other personal hygiene activities.

# ULCERE DE BURULI

# PIAN

# LEPRE

## Ofloxacin resistance in multibacillary new leprosy cases from Purulia, West Bengal: A threat to effective secondary line treatment for rifampicin resistant leprosy cases.

**Ahuja, M., Singh, I., Lavania, M., Pathak, V., Darlong, J., Turankar, R., Hembrom, S., Singh, S., Sengupta, U.**
15-06-2022
*J Glob Antimicrob Resist*
https://pubmed.ncbi.nlm.nih.gov/35717020

**Objective:** Purulia is one of the high endemic districts for leprosy in West Bengal [Eastern part of India]. The annual new case detection rate (ANCDR) of leprosy in West Bengal is 6.04/100000 (DGHS 2019-20). Our earlier report has already provided the evidence of presence of secondary drug resistance in relapse cases of leprosy. The primary aim of the study was to find out primary drug resistance pattern for dapsone, rifampicin and ofloxacin among new leprosy patients from Purulia, West Bengal. to find out the emergence of primary drug resistance to any of these drugs. **Methods:** In the present study, slit- skin smear samples were collected from 145 newly diagnosed leprosy cases from TLM Purulia hospital during the duration between 2017-2018. DNA was extracted from these samples and were analyzed for the genes associated with drug resistance in M. leprae genome by PCR and was followed by Sanger sequencing. Wild-type strain (Thai-53) and mouse footpad-derived drug-resistant (Z-4) strain was used as reference strains. **Results:** Out of 145 cases; 25 cases had shown mutation in any of the three genes of rpoB, folP and gyrA associated with rifampicin, dapsone and ofloxacin resistance as described by WHO respectively by Sanger sequencing. Among these 25 cases; 16 cases had shown the mutations in ofloxacin, 2 cases had shown the mutation in combination of ofloxacin and rifampicin, 4 cases had shown the mutation only in rifampicin, 1 case had shown mutation in combination of rifampicin and dapsone and 2 cases had shown mutation only in dapsone. **Discussion and conclusion:** Results from this study indicated the emergence of resistance to anti-leprosy drugs in new cases of leprosy. As ofloxacin is the alternate drug for the treatment of rifampicin resistant cases, the emergence of new cases with resistance to ofloxacin indicates that ofloxacin resistant M. leprae strains are actively circulating in endemic region i. e. Purulia, West Bengal of India and poses a concern about the effective treatment of rifampicin resistance cases.

## Social participation restriction among persons with leprosy discharged from a multidrug therapy clinic in northern Nigeria.

**Dahiru, T., Iliyasu, Z., Aliyu, M.**
17-06-2022
*Trans R Soc Trop Med Hyg*
https://pubmed.ncbi.nlm.nih.gov/35713983

**Background:** The burden of leprosy-related disability, stigma and social participation after completing treatment is not well documented in Nigeria. We assessed the extent of disability, level of stigma and predictors of activity limitation and social participation restriction after completing multidrug therapy (MDT) for leprosy in Kano, Nigeria. **Methods:** A consecutively recruited cross-section of 354 persons discharged from MDT and 360 community members were interviewed. The Eyes, Hands and Feet sum score, Screening of Activity Limitation and Safety Awareness scale, Participation scale and Jacoby Stigma scale were used for affected persons. The Exploratory Model Interview Catalogue scale was used to assess community-perceived stigma. Levels of disability, activity limitation, participation restriction and stigma were scored. Adjusted ORs for predictors were generated from logistic regression models. **Results:** Most (91.5%, n=324) respondents had a disability; (8.2%, n=29) and (83.3%, n=295) were WHO grades 1 and 2, respectively. Similarly, 321 participants (90.7%) had activity limitation and 316 respondents (89.3%) experienced participation restriction. Further, 88.7% of participants (n=314) anticipated stigma. Activity limitation was higher among unemployed participants, men, persons with disability and those who anticipated stigma. Participation restriction was higher among low income earners (≤1000 Nigerian Naira per month (equivalent to US$2.50 per month)) and persons with disability, limited activity and anticipated stigma. **Conclusion:** Leprosy-related disability, stigma, activity limitation and social participation restriction are high after treatment. We recommend community-based rehabilitation to sustain self-care, reduce stigma and ensure social inclusion.

## Elevated IL-23 in skin promotes IL-23 derived Th17 responses in leprosy patients.

**Shi, C., Ma, S., Bai, J., Liu, Y., Ma, Y., Lu, X., Zhu, J., Yang, D.**
15-06-2022
*Clin Exp Pharmacol Physiol*
https://doi.org/10.1111/1440-1681.13689

Leprosy is an infectious disease caused by non-cultivable

bacteria Mycobacterium leprae. Th17 cells play vital roles during pathogenesis of leprosy reactions and IL-23 is involved in Th17 cell differentiation. Although previous studies have reported the participation of IL-23 in leprosy patients in peripheral blood, the role of this cytokine in skin has not yet been described for the disease. In this study, we first evaluated IL-23 expression in the skin of patients with leprosy. Data showed that in keratinocytes, endothelial cells, and macrophages, IL-23 expression was markedly higher in patients compared to that in the normal skin controls. Also, leprosy patients presented higher percentage of IL-17A-producing IL-23R+CD4 T cells than healthy donors. IL-23R blocking induced markedly downregulated IL-17A secretion in leprosy patients but not in healthy donors. Furthermore, TGF-β expression was significantly elevated after IL-23R blocking. Overall, this study establishes that Th17 cells produce IL-17A in an IL-23 dependent manner in the skin of leprosy patients and provides more focused treatment strategies for Mycobacterium leprae. 

# TRYPANOSOMES (TRYPANOSOMIASE ET MALADIE DE CHAGAS)

## Characterization of triatomine bloodmeal sources using direct Sanger sequencing and amplicon deep sequencing methods.

**Balasubramanian, S., Curtis-Robles, R., Chirra, B., Auckland, L., Mai, A., Bocanegra-Garcia, V., Clark, P., Clark, W., Cottingham, M., Fleurie, G., Johnson, C., Metz, R., Wang, S., Hathaway, N., Bailey, J., Hamer, G., Hamer, S.**
17-06-2022
*Sci Rep*
https://doi.org/10.1038/s41598-022-14208-8

Knowledge of host associations of blood-feeding vectors may afford insights into managing disease systems and protecting public health. However, the ability of methods to distinguish bloodmeal sources varies widely. We used two methods-Sanger sequencing and amplicon deep sequencing-to target a 228 bp region of the vertebrate Cytochrome b gene and determine hosts fed upon by triatomines (n = 115) collected primarily in Texas, USA. Direct Sanger sequencing of PCR amplicons was successful for 36 samples (31%). Sanger sequencing revealed 15 distinct host species, which included humans, domestic animals (Canis lupus familiaris, Ovis aries, Gallus gallus, Bos taurus, Felis catus, and Capra hircus), wildlife (Rattus rattus, Incilius nebulifer, Sciurus carolinensis, Sciurus niger, and Odocoileus virginianus), and captive animals (Panthera tigris, Colobus spp., and Chelonoidis carbonaria). Samples sequenced by the Sanger method were also subjected to Illumina MiSeq amplicon deep sequencing. The amplicon deep sequencing results (average of 302,080 usable reads per sample) replicated the host community revealed using Sanger sequencing, and detected additional hosts in five triatomines (13.9%), including two additional blood sources (Procyon lotor and Bassariscus astutus). Up to four bloodmeal sources were detected in a single triatomine (I. nebulifer, Homo sapiens, C. lupus familiaris, and S. carolinensis). Enhanced understanding of vector-host-parasite networks may allow for integrated vector management programs focusing on highly-utilized and highly-infected host species.

## Potential distributions of the parasite Trypanosoma cruzi and its vector Dipetalogaster maxima highlight areas at risk of Chagas disease transmission in Baja California Sur, Mexico, under climate change.

**Flores-López, C., Moo-Llanes, D., Romero-Figueroa, G., Guevara-Carrizales, A., López-Ordoñez, T., Casas-Martínez, M., Samy, A.**
20-06-2022
*Med Vet Entomol*
https://doi.org/10.1111/mve.12591

Dipetalogaster maxima is a primary vector of Chagas disease in the Cape region of Baja California Sur, Mexico. The geographic distribution of D. maxima is limited to this small region of the Baja California Peninsula in Mexico. Our study aimed to construct the ecological niche models (ENMs) of this understudied vector species and the parasite responsible for Chagas disease (Trypanosoma cruzi). We modelled the ecological niches of both species under current and future climate change projections in 2050 using four Representative Concentration Pathways (RCPs): RCP 2.6, RCP 4.5, RCP 6.0, and RCP 8.5. We also assessed the human population at risk of exposure to D. maxima bites, the hypothesis of ecological niche equivalency and similarity between D. maxima and T. cruzi, and finally the abundance centroid hypothesis. The ENM predicted a higher overlap between both species in the Western and Southern coastal regions of the Baja California Peninsula. The climate change scenarios predicted a Northern shift in the ecological niche of both species. Our findings suggested that the highly tourist destination of Los Cabos is a high-risk zone for Chagas disease circulation. Overall, the study provides valuable data to vector surveillance and control programs.

## A New Record of the Introduced Species Triatoma infestans (Hemiptera: Reduviidae) in Mexico.

**Martínez-Hernández, F., Villalobos, G., Montañez-Valdez, O., Martínez-Ibarra, J.**
18-06-2022
*J Med Entomol*
https://pubmed.ncbi.nlm.nih.gov/35716079

Here, we report a new record of Triatoma infestans (Klug) in Mexico after 50 years and provide a brief description of the discovery area. Fifty-nine specimens (71.2% adults) of the introduced species were collected from the peridomestic areas of a single house in the port of Manzanillo in the state of Colima, Mexico. Thirty-one specimens (52.5%) were collected

from the exterior walls of the house and were apparently attracted to light. The other specimens (47.5%) were associated with chickens. No specimen was infected with Trypanosoma cruzi Chagas, the causative agent of Chagas disease, possibly because they were feeding on chickens. We speculate that the introduced species travelled from South America to Mexico via seed shipment in a twenty-foot equivalent unit (TEU) maritime container. Because Mexican phytosanitary regulations demand only the cargo to be inspected, the triatomines could have escaped notice during inspection. Subsequently, as the cargo was unloaded and the TEU was stored, the triatomines likely flew to and invaded the nearby residential areas. The rediscovery of this domestic vector of T. cruzi in Mexico warrants further investigation owing to the potential risk of transmission to the inhabitants of the study area.

## How to get away with murder: The multiple strategies employed by pathogenic protozoa to avoid complement killing.

Revue de littérature

**Rios-Barros, L., Silva-Moreira, A., Horta, M., Gontijo, N., Castro-Gomes, T.**
13-06-2022
*Mol Immunol*
https://pubmed.ncbi.nlm.nih.gov/35709630

Parasitic protozoa are eukaryotic unicellular organisms that depend on a variety of living organisms and can develop intra- and extracellularly inside their hosts. In humans, these parasites cause diseases with a significant impact on public health, such as malaria, toxoplasmosis, Chagas disease, leishmaniasis and amebiasis. The ability of a parasite in establishing a successful infection depends on a series of intricate evolutionarily selected adaptations, which include the development of molecular and cellular strategies to evade the host immune system effector mechanisms. The complement system is one of the main effector mechanisms and the first humoral shield of hosts innate immunity against pathogens. For unicellular pathogens, such as protozoa, bacteria and fungi, the activation of the complement system may culminate in the elimination of the invader mainly via 1- the formation of a pore that depolarizes the plasma membrane of the parasite, causing cell lysis; 2- opsonization and killing by phagocytes; 3- increasing vascular permeability while also recruiting neutrophils to the site of activation. Numerous strategies to avoid complement activation have been reported for parasitic protozoa, such as 1- sequestration of complement system regulatory proteins produced by the host, 2- expression of complement system regulatory proteins, 3- proteolytic cleavage of different complement effector molecules, 4- formation of a physical glycolipid barrier that prevents deposition of complement molecules on the plasma membrane, and 5- removal, by endocytosis, of complement molecules bound to plasma membrane. In this review, we revisit the different strategies of blocking various stages of complement activation described for the main species of parasitic protozoa, present the most recent discoveries in the field and discuss new perspectives on yet neglected strategies and possible new evasion mechanisms.

## Effect of clinician information sessions on diagnostic testing for Chagas disease.

**Mahoney West, H., Milliren, C., Manne-Goehler, J., Davis, J., Gallegos, J., Perez, J., Köhler, J.**
16-06-2022
*PLoS Negl Trop Dis*
https://doi.org/10.1371/journal.pntd.0010524

Background: Chagas disease is a potentially life-threatening neglected disease of poverty that is endemic in continental Latin America. Caused by Trypanosoma cruzi (T. cruzi), it is one of six parasitic diseases in the United States targeted by the Centers for Disease Control as a public health problem in need of action. An estimated 300,000 people are infected with T. cruzi in the United States (US). Although its morbidity, mortality and economic burden are high, awareness of Chagas disease is lacking among many healthcare providers in the US. The purpose of this analysis is to determine if the number of diagnostic tests performed at a community health center serving an at-risk population for Chagas disease increased after information sessions. A secondary aim was to determine if there was a difference by provider type, i.e., nurse practitioner vs. physician, or by specialty in the number of patients screened. Methodology/Principal findings: We conducted a retrospective data analysis of the number of Chagas serology tests performed at a community health center before and after information sessions for clinicians. A time series analysis was conducted focusing on the Adult and Family Medicine Departments at East Boston Neighborhood Health Center (EBNHC). Across all departments there were 1,957 T. cruzi tests performed before the sessions vs. 2,623 after the sessions. Interrupted time series analysis across departments indicated that testing volume was stable over time prior to the sessions (pre-period slope = +4.1 per month; p = 0.12), followed by an immediate shift after the session (+51.6; p = 0.03), while testing volume remained stable over time after the session (post-period slope = -6.0 per month; p = 0.11). Conclusion/Significance: In this study, Chagas testing increased after information sessions. Clinicians who began testing their patients for Chagas disease after learning of the importance of this intervention added an extra, potentially time-consuming task to their already busy workdays without external incentives or recognition.

## Towards environmental detection of Chagas disease vectors and pathogen.

**Gysin, G., Urbano, P., Brandner-Garrod, L., Begum, S., Kristan, M., Walker, T., Hernández, C., Ramírez, J., Messenger, L.**
14-06-2022
*Sci Rep*
https://doi.org/10.1038/s41598-022-14051-x

Chagas disease vector control relies on prompt, accurate identification of houses infested with triatomine bugs for

targeted insecticide spraying. However, most current detection methods are laborious, lack standardization, have substantial operational costs and limited sensitivity, especially when triatomine bug densities are low or highly focal. We evaluated the use of FTA cards or cotton-tipped swabs to develop a low-technology, non-invasive method of detecting environmental DNA (eDNA) from both triatomine bugs and Trypanosoma cruzi for use in household surveillance in eastern Colombia, an endemic region for Chagas disease. Study findings demonstrated that Rhodnius prolixus eDNA, collected on FTA cards, can be detected at temperatures between 21 and 32 °C, when deposited by individual, recently blood-fed nymphs. Additionally, cotton-tipped swabs are a feasible tool for field sampling of both T. cruzi and R. prolixus eDNA in infested households and may be preferable due to their lower cost. eDNA detection should not yet replace current surveillance tools, but instead be evaluated in parallel as a more sensitive, higher-throughput, lower cost alternative. eDNA collection requires virtually no skills or resources in situ and therefore has the potential to be implemented in endemic communities as part of citizen science initiatives to control Chagas disease transmission.

### Efficient CRISPR-Cas9-mediated genome editing for characterization of essential genes in *Trypanosoma cruzi*.

**Picchi-Constante, G., Hiraiwa, P., Marek, M., Rogerio, V., Guerra-Slompo, E., Romier, C., Zanchin, N.**
21-04-2022
*STAR Protoc*
https://doi.org/10.1016/j.xpro.2022.101324

This protocol outlines a new genetic complementation strategy to investigate gene function in *Trypanosoma cruzi*, the parasite causing Chagas disease. We combine CRISPR-Cas9 technology with recombination of variants of the target gene containing the desired mutations that are resistant to Cas9-cleavage, which enables detailed investigation of protein function. This experimental strategy overcomes some of the limitations associated with gene knockouts in *T. cruzi*. For complete details on the use and execution of this protocol, please refer to Marek et al. (2021).

## LEISHMANIOSE

### Probing O-substituted Nifuroxazide analogues against Leishmania: Synthesis, in vitro efficacy, and hit/lead identification.

**Badenhorst, G., Kannigadu, C., Aucamp, J., N'Da, D.**
19-06-2022
*Eur J Pharm Sci*
https://pubmed.ncbi.nlm.nih.gov/35732232

Leishmaniasis is a neglected tropical disease affecting millions of people worldwide, with 650 000 to 1.1 million new infections reported annually by the World Health Organization. Current antileishmanial treatments are unsatisfactory due to the development of parasitic resistance and the toxicity associated with the drugs used, and this highlights the need for the development of new antileishmanial drugs. In this study, a series of nifuroxazide analogues were synthesized in a single step reaction and investigated for their antileishmanial potential. The sulfonate 1l, bearing pyridine ring, was deemed an antileishmanial hit, targeting the amastigotes of Leishmania (L.) donovani and L. major, the pathogens of visceral and cutaneous leishmaniasis, respectively, with micromolar potencies. The benzyl analogues 2c and 2d were also confirmed as submicromolar active leads against amastigotes of L. major. These analogues stand as promising candidates for further investigation involving the evaluation of their in vivo activities and molecular targets.

### Treatment outcome of imported cutaneous leishmaniasis among travellers and migrants infected with Leishmania major and Leishmania tropica: a retrospective study in European centres 2013 to 2019.

**Glans, H., Dotevall, L., Van der Auwera, G., Bart, A., Blum, J., Buffet, P., Guery, R., Gangneux, J., van Henten, S., Harms, G., Varani, S., Robert-Gangneux, F., Rongisch, R., Andersson, B., Bradley, M.**
18-06-2022
*Int J Infect Dis*
https://pubmed.ncbi.nlm.nih.gov/35728749

Objectives: Cutaneous leishmaniasis (CL) in Asia, Northern and Sub-Saharan Africa is mainly caused by Leishmania major and Leishmania tropica. We describe and evaluate the treatment outcome of CL among travellers and migrants in Europe. Methods: A retrospective study of parasitological confirmed CL cases caused by L. major and L. tropica during 2013-2019 in Europe. Data were collected from medical records and databases within the LeishMan network. Results: Out of 206 included cases of CL, seventy-five were identified as L. major and 131 as L. tropica. Eighty percent of the patients with L. tropica infection were migrants, whereas 53 % of patients with L. major infection had been visiting friends and relatives. Among patients with L. tropica, 48 %, were younger than 15. Pentavalent antimony cured 73 % (L. major) and 78 % (L. tropica). Intralesional administration had a cure rate, 86 % and systemic, 67%, on L. tropica. Liposomal amphotericin B had a cure rate of 44-63 %. Conclusion: L. major infections were mostly found in individuals visiting friends and relatives, whereas L. tropica were mainly identified in migrants. No patients with L. major relapsed. Pentavalent antimony, liposomal amphotericin B and cryotherapy had cure rates in accordance with previous studies.

### Livestock infected with Leishmania spp. in southern Iran.

**Rezaei, Z., Pourabbas, B., Asaei, S., Sepehrpour, S., Ahmadnia**

**Motlagh, S., Pourabbas, P., Abdolahi Khasibi, S., Alborzi, A.**
17-06-2022
*Parasit Vectors*
https://doi.org/10.1186/s13071-022-05313-8

Background: The magnitude of the health problems caused by leishmaniasis has been a major driving factor behind the development and implementation of leishmaniasis control programs by the national authorities in Iran, with a priority for health and environmental management. Such programs are not achievable unless all of the factors leading to the infection, including the parasite's life-cycle, vectors and reservoirs, are recognized. So far in Iran, humans and rodents have been considered the principal reservoirs of Leishmania tropica and Leishmania major, respectively, both associated with cutaneous leishmaniasis (CL), with domestic dogs considered to be the main reservoir for Leishmania infantum, associated with visceral leishmaniasis (VL). The role of other mammals in maintaining the Leishmania parasite has remained unclear. This study aimed to investigate Leishmania infection among livestock in endemic areas of VL and CL in Fars province, southern Iran, using serological and molecular methods. Methods: Blood samples from 181 clinically healthy livestock, including 49 sheep, 114 goats, 16 cattle and two donkeys, were screened to detect Leishmania DNA and anti-Leishmania antibodies using qPCR (quantitative PCR) and the direct agglutination test (DAT), respectively. Four qPCR-positive samples were amplified using the internal transcribed spacer one (ITS1) primers in conventional PCR and sent for directional sequencing. Results: Of the 181 livestock tested, 51 (28.2%) were infected with Leishmania, using serological and molecular methods. Anti-Leishmania antibodies were detected in 70 (38.7%) (95% confidence interval [CI]: 31.5-46.2) and Leishmania DNA in 93 (51.4%) (95% CI: 43.9-58.9) livestock. The identified Leishmania spp. were L. infantum and L. major. Conclusions: The findings of the present study show a relatively high prevalence of Leishmania infection among livestock in endemic areas of the disease, in Fars province, southern Iran. Given the large population of this group of animals and the fact that they live in the vicinity of the main reservoirs of the disease and vectors, it seems that sand flies regularly bite these animals. Further studies are needed to determine the role of livestock in the parasite's life-cycle and the epidemiology of Leishmania infection.

## Nanomedicine-based strategies to improve treatment of cutaneous leishmaniasis.

**Goonoo, N., Laetitia Huët, M., Chummun, I., Karuri, N., Badu, K., Gimié, F., Bergrath, J., Schulze, M., Müller, M., Bhaw-Luximon, A.**
15-06-2022
*R Soc Open Sci*
https://doi.org/10.1098/rsos.220058

Nanomedicine strategies were first adapted and successfully translated to clinical application for diseases, such as cancer and diabetes. These strategies would no doubt benefit unmet diseases needs as in the case of leishmaniasis. The latter causes skin sores in the cutaneous form and affects internal organs in the visceral form. Treatment of cutaneous leishmaniasis (CL) aims at accelerating wound healing, reducing scarring and cosmetic morbidity, preventing parasite transmission and relapse. Unfortunately, available treatments show only suboptimal effectiveness and none of them were designed specifically for this disease condition. Tissue regeneration using nano-based devices coupled with drug delivery are currently being used in clinic to address diabetic wounds. Thus, in this review, we analyse the current treatment options and attempt to critically analyse the use of nanomedicine-based strategies to address CL wounds in view of achieving scarless wound healing, targeting secondary bacterial infection and lowering drug toxicity.

## Pamidronate, a promising repositioning drug to treat leishmaniasis, displays antileishmanial and immunomodulatory potential.

**Ribeiro, J., Rodrigues-Alves, M., Oliveira, E., Guimarães, P., Maria Murta Santi, A., Teixeira-Carvalho, A., Murta, S., Peruhype-Magalhães, V., Souza-Fagundes, E.**
15-06-2022
*Int Immunopharmacol*
https://pubmed.ncbi.nlm.nih.gov/35716482

Visceral leishmaniasis (VL) is an infectious disease caused by Leishmania infantum (L. infantum). Currently, there are no vaccines and/or prophylactic therapies against VL, and the recentpharmacological approaches come from the drug repositioning strategy. Here, we evaluated the anticancer drug pamidronate (PAM) to identify a new therapeutic option for the treatment of human VL. We assessed its in vitro antileishmanial activity against the promastigote and amastigote forms of L. infantum by evaluating cell cytotoxicity. The antileishmanial and immunomodulatory activities were assessed using human peripheral blood leukocytes ex vivo. PAM induced the formation of vacuoles in the cytoplasm of the promastigotes and alterations in the morphology of the kinetoplast and mitochondria in vitro, which indicates anti-promastigote activity. PAM also reduced the number of infected macrophages and intracellular amastigotes in a concentration-dependent manner, with cell viability above 70%. In ex vivo, PAM reduced the internalized forms of L. infantum in the classical monocyte subpopulation. Furthermore, it enhanced IL-12 and decreased IL-10 and TGF-β by monocytes and neutrophils. Increased IFN-γ and TNF levels for $CD8^-$ and $CD8^+$ T lymphocytes and B lymphocytes, respectively, were observed after the treatment with PAM, as well as a reduction in IL-10 by the lymphocyte subpopulations evaluated. Taken together, our results suggest that PAM may be eligible as a potential therapeutic alternative for drug repurposing to treat human visceral leishmaniasis.

## Comparison of serum cytokine levels in symptomatic and asymptomatic HIV-Leishmania coinfected individuals from a Brazilian visceral leishmaniasis endemic area.

**Guedes, D., Silva, E., Castro, M., Júnior, W., Ibarra-Meneses, A., Tsoumanis, A., Adriaensen, W., van Griensven, J., Pereira, V., Medeiros, Z.**
17-06-2022
*PLoS Negl Trop Dis*
https://doi.org/10.1371/journal.pntd.0010542

**Background:** Visceral leishmaniasis (VL) remains an important infectious disease worldwide. VL-HIV coinfected individuals can present with atypical clinical forms of VL and have a high risk of VL relapse. Some cytokines have been described as potential markers to diagnose active VL and to predict the severity of the cases. However, few studies have included VL-HIV coinfected patients. We aimed to characterize the levels of several cytokines among VL-HIV coinfected individuals living in a VL-endemic area in Northeast Brazil. **Methods:** This was a retrospective, cross-sectional study, aiming to estimate the levels of various cytokines in symptomatic and asymptomatic VL-HIV coinfected individuals. There were 134 study participants (35 symptomatic VL-HIV, 75 asymptomatic VL-HIV, and 24 healthy controls), all ≥ 18 years-old. Serum cytokine levels (interferon-γ, tumor necrosis factor, and interleukins 2, 4, 6, 10, and 17A) were quantified using the Becton Dickinson-BD's Cytometric Bead Array (CBA) system. **Results:** The population mainly consisted of men (64.9%), with a median age of 35 (27-41) years. Asymptomatic individuals were younger ($p = 0.013$), with more years of education ($p < 0.001$), and were more often on antiretroviral therapy ($p < 0.001$) than those in the symptomatic group. Hemoglobin levels ($p < 0.001$), lymphocytes ($p < 0.001$) and CD4 count ($p < 0.001$) were lower in symptomatic individuals, while HIV viral loads were higher ($p < 0.001$). In the symptomatic VL-HIV coinfected group, we observed increased serum levels of IL-17A, IL-6, and IL-10 compared to asymptomatic patients and the healthy controls. There were no differences in the levels of all cytokines between asymptomatic VL-HIV coinfected individuals and the healthy controls. **Conclusions:** Higher serum levels of IL-17A, IL-6, and IL-10 cytokines were observed in symptomatic coinfected individuals but not in asymptomatically infected individuals. More studies among HIV-positive persons are needed to better understand the role of serum cytokines for prognosis, to define cure and predict VL relapses in VL-HIV coinfected individuals.

## The role of ATP-binding cassette transporter genes expression in treatment failure cutaneous leishmaniasis.

**Boozhmehrani, M., Eslami, G., Khamesipour, A., Jafari, A., Vakili, M., Hosseini, S., Askari, V.**
16-06-2022
*AMB Express*
https://doi.org/10.1186/s13568-022-01419-5

Leishmaniasis is one of the common diseases transmitted by sand flies in tropical and subtropical regions of the world. Currently, antimonial derivatives are the first line of treatment. Some of the members of the ATP-binding cassette (ABC) family of Leishmania are shown to be associated with no response to treatment. In this study, we evaluated ABCI4, ABCG2, ABCC7, ABCB4, and ABCC3 genes expression in Leishmania isolated from patients with non-healing cutaneous leishmaniasis and treatment response isolates. We selected 17 clinical isolates including 8 treatment failure and 9 treatment response samples from September 2020 to March 2021. The isolates were obtained from patients of Health Center Laboratory of Varzaneh, Isfahan, Iran with cutaneous leishmaniasis. The diagnosis was performed using microscopic observation. The samples were directly collected from the lesions. The expression profiling of genes was assessed using SYBR Green real-time PCR that was analyzed with delta-delta Ct. All treatment failure clinical isolates were L. major. Gene expression analysis in treatment failure isolates showed that the ABC transported genes had a different pattern in each isolate. Treatment failure has been reported for cutaneous leishmaniasis worldwide. Knowledge of the molecular mechanisms of treatment failure could solve this problem. ABC transporter genes are considered controversial over the mechanisms of treatment failure outcomes. In this study, we showed that ABC transporter genes could be considered one of the important mechanisms.

## Structural basis of rapid actin dynamics in the evolutionarily divergent Leishmania parasite.

**Kotila, T., Wioland, H., Selvaraj, M., Kogan, K., Antenucci, L., Jégou, A., Huiskonen, J., Romet-Lemonne, G., Lappalainen, P.**
15-06-2022
*Nat Commun*
https://doi.org/10.1038/s41467-022-31068-y

Actin polymerization generates forces for cellular processes throughout the eukaryotic kingdom, but our understanding of the 'ancient' actin turnover machineries is limited. We show that, despite>1 billion years of evolution, pathogenic Leishmania major parasite and mammalian actins share the same overall fold and co-polymerize with each other. Interestingly, Leishmania harbors a simple actin-regulatory machinery that lacks cofilin 'cofactors', which accelerate filament disassembly in higher eukaryotes. By applying single-filament biochemistry we discovered that, compared to mammalian proteins, Leishmania actin filaments depolymerize more rapidly from both ends, and are severed>100-fold more efficiently by cofilin. Our high-resolution cryo-EM structures of Leishmania ADP-, ADP-Pi- and cofilin-actin filaments identify specific features at actin subunit interfaces and cofilin-actin interactions that explain the unusually rapid dynamics of parasite actin filaments. Our findings reveal how divergent parasites achieve rapid actin dynamics using a remarkably simple set of actin-binding proteins, and elucidate evolution of the actin cytoskeleton.

## Therapeutic effects of Lucilia sericata larval excretion/secretion products on Leishmania major under in vitro and in vivo conditions.

**Sherafati, J., Dayer, M., Ghaffarifar, F.**
16-06-2022
*Parasit Vectors*

https://doi.org/10.1186/s13071-022-05322-7

**Background:** Leishmaniasis is a neglected infectious disease caused by protozoa of the genus Leishmania. The disease generally manifests as characteristic skin lesions which require lengthy treatment with antimonial drugs that are often associated with adverse side effects. Therefore, a number of studies have focused on natural compounds as promising drugs for its treatment. This study aimed to evaluate the effects of larval excretion/secretion products (ES) of Lucilia sericata in crude and fractionated forms on Leishmania major, by using in vitro and in vivo models. **Methods:** The in vitro experiments involved evaluation of ES on both promastigotes and macrophage-engulfed amastigotes, whereas the in vivo experiments included comparative treatments of skin lesions in L. major-infected mice with Eucerin-formulated ES and Glucantime. **Results:** The half maximal inhibitory concentrations of the crude ES, > 10-kDa ES fraction, < 10-kDa ES fraction, and Glucantime were 38.7 µg/ml, 47.6 µg/ml, 63.3 µg/ml, and 29.1 µg/ml, respectively. Significant differences were observed between percentage viabilities of promastigotes treated with the crude ES and its fractions compared with the negative control ($P<0.0001$). The crude ES was more effective on amastigotes than the two ES fractions at 300 µg/ml. The macroscopic measurements revealed that the reduction of lesion size in mice treated with the crude ES followed quicker cascades of healing than that of mice treated with Glucantime and the ES fractions. **Conclusions:** The present study showed that the larval ES of L. sericata in both crude and fractionated forms are effective for both intracellular and extracellular forms of L. major. Also, the ES exert both topical and systemic effects on mice experimentally infected with L. major.

## Molecular detection of Leishmania infantum in rats and sand flies in the urban sewers of Barcelona, Spain.

**Galán-Puchades, M., Solano, J., González, G., Osuna, A., Pascual, J., Bueno-Marí, R., Franco, S., Peracho, V., Montalvo, T., Fuentes, M.**
16-06-2022
*Parasit Vectors*
https://doi.org/10.1186/s13071-022-05309-4

**Background:** Classically, dogs have been considered to be the only reservoir of leishmaniasis in urban areas. However, in a previous study, we found a 33.3% prevalence of Leishmania infantum in the spleens of Norway rats (Rattus norvegicus) sampled in the underground sewer system of the city of Barcelona (Spain). The aim of the present study was to verify, using molecular methods, the potential reservoir role of these rats in the same sewer system. **Methods:** A sensitive real-time PCR (qPCR) assay, DNA sequencing and phylogenetic analysis were carried out to identify and quantify the presence of L. infantum DNA in sand fly individuals captured in the same underground sewer system of Barcelona as in our previous study and in the spleens and ears of rats captured in the same sewer system. **Results:** Leishmania infantum DNA was found in 14 of the 27 (51.9%) sand flies identified as Phlebotomus perniciosus, and 10 of the 24 (41.7%) rats studied were infected. Leishmania infantum was found in the spleens (70%) and in the ears (40%) of the infected rats. Quantitative results revealed the presence of high loads of L. infantum in the rats studied (> $3\times10^6$ parasites/g ear tissue) and among the sand flies (> $34\times10^6$ parasites in 1 individual). **Conclusions:** The molecular methods used in this study demonstrated a high prevalence of L. infantum in the underground sewer populations of both R. norvegicus and P. perniciosus. These results suggest that sewer rats, in addition to dogs, are likely to act as reservoirs of leishmaniasis in cities, where sewer systems seem to offer the ideal scenario for the transmission of leishmaniasis. Therefore, to achieve the WHO 2030 target on the elimination of leishmaniasis as a public health problem successfully, an efficient control strategy against leishmaniasis in rats and sand flies should be implemented, particularly in the sewer systems of urban areas of endemic countries.

## A structural vaccinology approach for in silico designing of a potential self-assembled nanovaccine against Leishmania infantum.

**Vakili, B., Nezafat, N., Negahdaripour, M., Ghasemi, Y.**
14-06-2022
*Exp Parasitol*
https://pubmed.ncbi.nlm.nih.gov/35709889

Visceral leishmaniasis (VL) remains a major public health problem across 98 countries. To date, VL has no effective drug. Vaccines, as the most successful breakthroughs in medicine, can promise an effective strategy to fight various diseases. More recently, self-assembled peptide nanoparticles (SAPNs) have attracted considerable attention in the field of vaccine design due to their multivalency. In this study, a SAPN nanovaccine was designed using various immunoinformatics methods. High-ranked epitopes were chosen from a number of antigens, including Leishmania-specific hypothetical protein (LiHy), Leishmania-specific antigenic protein (LSAP), histone H1, and sterol 24-c-methyltransferase (SMT). To facilitate the oligomerization process, pentameric and trimeric coiled-coil domains were employed. RpfE, a resuscitation-promoting factor of Mycobacterium tuberculosis, was added to induce strong immune responses. Pentameric and trimeric coiled-coil domains as well as eight immunodominant epitopes from antigenic proteins of Leishmania infantum, the causative agent of VL, were joined together using appropriate linkers. High-quality 3D structure of monomeric and oligomeric structures followed by refinement and validation processes demonstrated that the designed nanovaccine could be considered to be a promising medication against the parasite; however, experimental validation is essential to confirm the effectiveness of the nanovaccine.

## How to get away with murder: The multiple strategies employed by pathogenic protozoa to avoid complement killing.

Revue de littérature

**Rios-Barros, L., Silva-Moreira, A., Horta, M., Gontijo, N., Castro-Gomes, T.**
13-06-2022
*Mol Immunol*
https://pubmed.ncbi.nlm.nih.gov/35709630

Parasitic protozoa are eukaryotic unicellular organisms that depend on a variety of living organisms and can develop intra- and extracellularly inside their hosts. In humans, these parasites cause diseases with a significant impact on public health, such as malaria, toxoplasmosis, Chagas disease, leishmaniasis and amebiasis. The ability of a parasite in establishing a successful infection depends on a series of intricate evolutionarily selected adaptations, which include the development of molecular and cellular strategies to evade the host immune system effector mechanisms. The complement system is one of the main effector mechanisms and the first humoral shield of hosts innate immunity against pathogens. For unicellular pathogens, such as protozoa, bacteria and fungi, the activation of the complement system may culminate in the elimination of the invader mainly via 1- the formation of a pore that depolarizes the plasma membrane of the parasite, causing cell lysis; 2- opsonization and killing by phagocytes; 3- increasing vascular permeability while also recruiting neutrophils to the site of activation. Numerous strategies to avoid complement activation have been reported for parasitic protozoa, such as 1- sequestration of complement system regulatory proteins produced by the host, 2- expression of complement system regulatory proteins, 3- proteolytic cleavage of different complement effector molecules, 4- formation of a physical glycolipid barrier that prevents deposition of complement molecules on the plasma membrane, and 5- removal, by endocytosis, of complement molecules bound to plasma membrane. In this review, we revisit the different strategies of blocking various stages of complement activation described for the main species of parasitic protozoa, present the most recent discoveries in the field and discuss new perspectives on yet neglected strategies and possible new evasion mechanisms.

## Evaluation of the inhibitory potential of Valproic acid against histone deacetylase of *Leishmania donovani* and computational studies of Valproic acid derivatives.

**Prasanna, P., Joshi, T., Pant, M., Pundir, H., Chandra, S.**
15-06-2022
*J Biomol Struct Dyn*
https://doi.org/10.1080/07391102.2022.2087103

Valproic acid (VA) is a proven inhibitor of human histone deacetylases (HDACs). The homogenous HDAC has been associated with all major human parasitic pathogens and hence, it has been considered an attractive drug target for anti-leishmanial therapy. To assist in drug design endeavors for HDACs, an in-*vitro* study has been presented to investigate the VA inhibition on *Leishmania donovani* HDAC (*Ld*HDAC). The regression analysis of VA by 24hrs viability assay confirmed its activity against *Ld*HDAC. Moreover, the toxicity of VA is also well documented. Thus, the *in-silico* experiments were also conducted to screen the non-toxic VA derivatives as anti-leishmanial drug candidates having potential as inhibitors of *Ld*HDAC. For *in-silico* study, the 3D structure of target *Ld*HDAC was developed by homology modeling. Based on their *in-silico* activity, we shortlisted 13 VA derivatives having maximum affinity for *Ld*HDAC and identified four potential derivatives that can specifically bind to this protein. After that, these ligands were subjected to molecular dynamics simulation. These derivatives may be effective against *L. donovani* promastigotes since they followed Lipinski's RO5 and were non-toxic. Thus, screened derivatives can be considered as lead ligands for targeting *Ld*HDAC and may be used as possible drug candidates to treat leishmaniasis and overcome the limitation of anti-leishmanial drugs. This is the first report of antileishmanial potential of VA and its derivatives targeting *Ld*HDAC. Hence, the current investigation presents a search for novel target specific drugs to aid the anti-leishmanial drug development. Communicated by Ramaswamy H. Sarma.

## Leishmania braziliensis causing human disease in Northeast Brazil presents loci with genotypes in long-term equilibrium.

**Silva, J., Pinheiro, A., Dourado, M., Medina, L., Queiroz, A., Guimarães, L., Lessa, M., Lago, E., Machado, P., Wilson, M., Carvalho, E., Schriefer, A.**
15-06-2022
*PLoS Negl Trop Dis*
https://doi.org/10.1371/journal.pntd.0010390

Background: Leishmaniases are neglected tropical diseases that inflict great burden to poor areas of the globe. Intense research has aimed to identify parasite genetic signatures predictive of infection outcomes. Consistency of diagnostic tools based on these markers would greatly benefit from accurate understanding of Leishmania spp. population genetics. We explored two chromosomal loci to characterize a population of L. braziliensis causing human disease in Northeast Brazil. Methodology/Principal findings: Two temporally distinct samples of L. braziliensis were obtained from patients attending the leishmaniasis clinic at the village of Corte de Pedra: (2008-2011) primary sample, N = 120; (1999-2001) validation sample, N = 35. Parasites were genotyped by Sanger's sequencing of two 600 base pairs loci starting at nucleotide positions 3,074 and 425,451 of chromosomes 24 and 28, respectively. Genotypes based on haplotypes of biallelic positions in each locus were tested for several population genetic parameters as well as for geographic clustering within the region. Ample geographic overlap of genotypes at the two loci was observed as indicated by non-significant Cusick and Edward's comparisons. No linkage disequilibrium was detected among combinations of haplotypes for both parasite samples. Homozygous and heterozygous genotypes displayed Hardy-Weinberg equilibrium (HWE) at both loci in the two samples when straight observed and expected counts were compared by Chi-square (p>0.5). However, Bayesian statistics using one million Monte-Carlo randomizations disclosed a less robust HWE for

chromosome 24 genotypes, particularly in the primary sample (p = 0.04). Fixation indices (Fst) were consistently lower than 0.05 among individuals of the two samples at both tested loci, and no intra-populational structuralization could be detected using STRUCTURE software. **Conclusions/Significance:** These findings suggest that L. braziliensis can maintain stable populations in foci of human leishmaniasis and are capable of robust genetic recombination possibly due to events of sexual reproduction during the parasite's lifecycle.

### Characterization of *Leishmania (L.) amazonensis* Oligopeptidase B and its role in macrophage infection.

**Barbosa, G., Marana, S., Stolf, B.**
15-06-2022
*Parasitology*
https://doi.org/10.1017/S0031182022000816

## CYSTICERCOSE

### [Correlation between clinical and tomographic variables in patients with neurocysticercosis. A study in a cohort of patients in Sierra Norte, Ecuador, between 2019 and 2020].

**Anaya-González, J., López-Muñoz, F., Carmona-Álvarez Builla, E., Miniet-Castillo, A.**
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*Rev Neurol*
https://pubmed.ncbi.nlm.nih.gov/35698433/

**Introduction:** Neurocysticercosis (NCC) is the most frequent parasitic disease in the central nervous system of humans. **Objective:** to establish the correlation between clinical and tomographic variables in patients with neurocysticercosis in the neurology consultation of Hospital San Vicente de Paul and Hospital IESS Ibarra, during the year 2020. **Patients and methods:** descriptive, correlational and cross-sectional research. 93 patients. **Population and sample:** The information was collected in the neurology consultation. Clinical and imaging criteria were used for diagnosis. Odds Ratio (OR; 95% CI) was calculated. For multivariate analysis, binary logistic regression models were used. Statistical significance was considered when the value of p <0.05. **Symptoms:** headache (77.4%), epilepsy (41.9%). Tomographic findings: size < 1 cm (67.7%), single lesion (54.8%), supratentorial (93.5%). There were several clinical / tomographic correlations in the bivariate analysis, the presence of epilepsy was associated with lesions of size >1 cm (OR: 9.65; 95% CI: 3.48-26.7), the vesicular + ventricular colloidal stage + nodular (OR: 3.90; 95% CI: 1.64-9.28) and parenchymal topography (OR: 5.03; 95% CI: 2.03-12.4) (p < 0.05). In the multivariate analysis, epilepsy was not associated with tomographic aspects such as the size, stage and topography of the cysticerci (p < 0.05). Headache and reduced muscle strength were associated with parenchymal topography and stage of lesions respectively (p < 0.05). **Conclusions:** Despite having a wide clinical spectrum, the presence of epilepsy, headache, and reduced muscle strength seem to be the most representative manifestations, so their inclusion in the development of prognostic scores should be evaluated, which allow evaluating the approach diagnostic and evolutionary in subsequent research.

## DRACUNCULOSE

## ECHINOCOCCOSE

### Tim-3/Galectin-9 signaling pathway is involved in the cytokine changes in mice with alveolar echinococcosis.

**Li, S., Zhu, Y., Wang, S., Li, Y., Pang, N., An, M., Zhang, F., Ding, J.**
17-06-2022
*Mol Biol Rep*
https://doi.org/10.1007/s11033-022-07554-3

**Background:** Tim-3/Galectin-9 is involved in the immune escape of many pathogens. However, the role of Tim-3/Galectin-9 in persistent infection of Echinococcus multilocularis (Em), which is related to immune escape, is still unclear. **Objective:** To investigate the role of Tim-3/Galectin-9 and related cytokines in mice with persistent infection of Em. **Methods:** Em infection model was established by injecting the protoscoleces. Serum was collected at days 2, 8, 30, 60, 90, 180 and 270 after infection. Lymphocytes were isolated from liver tissue samples with Ficoll. Tim-3+CD4+T percentage was analyzed by flow cytometry. CD4+T cells were isolated from liver tissues of Em infected mice and cultured in vitro. The mRNA levels of Tim-3, Galectin-9, IFN-γ and IL-4 were detected by qRT-PCR. Cytokine levels in serum and culture supernatant (IFN-γ and IL-4) were analyzed by cytometric bead array. **Results:** The expression of Tim-3 and Galectin-9 mRNA significantly increased after 30 days of infection, reached peak on day 90, and then decreased slightly on days 180-270. The expression of IFN-γ mRNA, increased on day 2 and 8 after infection, slightly decreased on days 30-60, and obvious decreased on days 90-270, but were still higher than those of the control group. The expression of IL-4 mRNA gradually increased along with the time of infection. In serum of Em infected mice, level of IFN-γ peaked at day 30 and then gradually decreased; whereas IL-4 level peaked at day 90 and then gradually decreased. In vitro experiment found that Tim-3/Galectin-9 directly caused the changes in the levels of IFN-γ and IL-4. **Conclusions:** Tim-3/Galectin-9 signaling pathway may be involved in the development of persistent infection of Em by regulating the production of Th1 and Th2 cytokines.

### A Case of Extensive Thoracolumbar Spinal Intradural Cystic Echinococcosis.

**Liu, P., Feng, H., Liu, J.**
14-06-2022
*World Neurosurg*
https://pubmed.ncbi.nlm.nih.gov/35714948

Spinal cystic echinococcosis (CE) is a rare but devastating form of a neglected parasitic disease caused by the larval stage of the cestode Echinococcus granulosus. CE or hydatid disease, most commonly affects the liver and lungs. Spinal CE occurs in less than 1% of all cases. Patients with cysts confined to the intradural space typically present with neurological impairment due to compression of the spinal cord. We report a case of a 32-year-old woman with unusual, extensive spinal intradural CE, located at the T2 to L5 levels. She was treated with surgical removal of the cystic lesions by laminectomy and instrumentation. Long term oral albendazole was recommended postoperatively. Her status was medically stable at 5-year follow up, but lower limbs paralysis, urinary retention and bowel dysfunction persisted.

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

### Transcriptomic and proteomic profiling of peptidase expression in Fasciola hepatica eggs developing at host's body temperature.

**Ilgová, J., Vorel, J., Roudnický, P., Škorpíková, L., Horn, M., Kašný, M.**
20-06-2022
*Sci Rep*
https://doi.org/10.1038/s41598-022-14419-z

Fasciola hepatica is a global parasite of livestock which also causes a neglected zoonosis in humans. The parasite's communication with the host during its complicated lifecycle is based on an ingenious enzymatic apparatus which includes a variety of peptidases. These enzymes are implicated in parasite migration, pathogenesis of the disease, and modification of host immune response. Although the dynamics of proteolytic machinery produced by intra-mammalian F. hepatica life stages has been previously investigated in great detail, peptidases of the eggs so far received little scientific attention. In this study, we performed a comparative RNA-seq analysis aimed at identification of peptidases expressed in F. hepatica eggs, cultured at 37 °C to represent gall bladder retained eggs, for different time periods and employed mass spectrometry in order to identify and quantify peptidases translated in F. hepatica egg lysates. We demonstrated that F. hepatica eggs undergo significant molecular changes when cultured at the physiological temperature of the definitive host. Egg transcriptome is subject to numerous subtle changes while their proteome is even more variable. The peptidase profile is considerably modified on both transcriptome and proteome level. Finally, we measured and classified proteolytic activities in extracts from F. hepatica eggs using a library of fluorogenic substrates and peptidase class-selective inhibitors. Activities of threonine peptidases were detected constantly, while the cysteine peptidases prevailing in freshly laid eggs are substituted by aspartic peptidase and metallopeptidase activities in the later stages of egg development.

### A case of cerebral paragonimiasis misdiagnosed as eosinophilic granulomatosis with polyangiitis.

**Yamamuro, S., Ohoni, S., Kamiya, K., Imamura, G., Harano, S., Tahara, J., Ooshima, H., Oinuma, T., Haraoka, H., Nakamura, H., Yoshino, A.**
20-06-2022
*Neuropathology*
https://doi.org/10.1111/neup.12841

Paragonimiasis is a parasitic disease caused by Paragonimus westermani infection, and migration to the brain results in cerebral paragonimiasis. Cerebral paragonimiasis is now extremely rare, but a few cases are still reported. A 48-year-old Japanese woman presented with right-hand convulsion, right-hand numbness, sputum, and fatigue. Chest computed tomography demonstrated multiple nodular lesions, and head computed tomography revealed a hemorrhagic lesion in the left motor cortex. Magnetic resonance imaging revealed multiple small ring-shaped lesions with surrounding edema. Laboratory evaluation demonstrated peripheral eosinophilia. We considered eosinophilic granulomatosis with polyangiitis and started steroid treatment as a diagnostic therapy since we wanted to avoid cerebral lesion biopsy if possible. However, the patient underwent craniotomy surgery after steroid treatment for four months because a new intracerebral mass lesion had appeared. Trematode eggs were detected in the sample, and the final diagnosis was cerebral paragonimiasis. The patient was successfully treated with praziquantel. Cerebral paragonimiasis is extremely rare but should be considered in the differential diagnosis if atypical intracranial hemorrhage and peripheral eosinophilia are observed.

### Geospatial analysis of the associations between environmental contamination with livestock feces and children with chronic fascioliasis in the Anta province of Cusco, Peru.

**Tanabe, M., Prochaska, J., Morales, M., Lopez, M., Baca-Turpo, B., Arque, E., Cabada, M.**
16-06-2022
*PLoS Negl Trop Dis*
https://doi.org/10.1371/journal.pntd.0010499

Fasciola hepatica is a neglected parasitic infection with significant human health and livestock industry impact. The

Andean Altiplano harbors an estimated 50% of the Fasciola's world infection burden. There is scarce data regarding the spatial associations between different Fasciola hosts. In this project, we aimed to determine the geospatial relationships between Fasciola eggs passed in feces of different livestock species and the risk of infection among each household as a unit. We used data from a cross-sectional study evaluating children and livestock feces for Fasciola infection around households in three districts of Anta province, in the Cusco region of Peru. Each sample was geographically tagged and evaluated for fascioliasis using microscopy methods. A total of 2070 households were included, the median age was 9.1 years (6.7-11.8), 49.5% were female, and 7.2% of the households had at least one infected child. A total of 2420 livestock feces samples were evaluated. The infection rate in livestock samples was 30.9%. The highest infection rate was found in sheep with 40.8%, followed by cattle (33.8%), and swine (26.4%). The median distance between a household with an infected child to a positive animal sample was 44.6 meters (IQR 14.7-112.8) and the distance between a household with no infected children to a positive animal sample was 62.2 meters (IQR 18.3-158.6) (p = 0.025). The multivariable logistic regression adjusted by presence of poor sanitation, unsafe water consumption, altitude, and presence of multiple infected children per household demonstrated an association between household infection and any cattle feces at a 50 meters radius (Uninfected: OR 1.42 (95%CI 1.07-1.89), p = 0.017. Infected: OR 1.89 (95%CI 1.31-2.73), p = 0.001), positive cattle feces at a 100 meters radius (OR 1.35 (95% CI 1.08-1.69), p = 0.008), and negative cattle feces at a 200 meters radius (OR 1.08 (95% CI 1.01-1.15), p = 0.022). We identified potential hot and cold spots for fascioliasis in the Anta province. An association between environmental contamination with feces from different livestock species and infected children in rural households was found in our study. Local health authorities may apply this strategy to estimate the risk of infection in human populations and apply targeted interventions.

### Current status of *Clonorchis sinensis* and clonorchiasis in Korea: epidemiological perspectives integrating the data from human and intermediate hosts.

Revue de littérature

**Yoo, W., Sohn, W., Na, B.**
14-06-2022
*Parasitology*
https://doi.org/10.1017/S0031182022000798

## FILARIOSE LYMPHATIQUE

## MYCETOME

## ONCHOCERCOSE

## SCHISTOSOMIASE

### A family cluster of schistosomiasis acquired in Solenzara River, Corsica (France) - Solenzara River is clearly a transmission site for schistosomiasis in Corsica.

**Wellinghausen, N., Moné, H., Mouahid, G., Nebel, A., Tappe, D., Gabriel, M.**
18-06-2022
*Parasitol Res*
https://doi.org/10.1007/s00436-022-07574-9

We report a patient with urogenital schistosomiasis and three cases of subclinical infection within one family acquired from Solenzara River, Corsica, in 2019. Our cases confirm that transmission of schistosomiasis in Corsica is ongoing and has been extended from the Cavu River to the Solenzara River. Solenzara River is clearly a transmission site for schistosomiasis in Corsica. Public health efforts are recommended to uncover and prevent further cases.

### Molecular evidence on the presence of Schistosoma japonicum infection in snails along the Yangtze River, 2015-2019.

**Li, Y., Dang, H., Guo, S., Zhang, L., Feng, Y., Ding, S., Shan, X., Li, G., Yuan, M., Xu, J., Li, S.**
18-06-2022
*Infect Dis Poverty*
https://doi.org/10.1186/s40249-022-00995-9

Background: Due to sustained control activities, the prevalence of Schistosoma japonicum infection in humans, livestock and snails has decreased significantly in P. R. China, and the target has shifted from control to elimination according to the Outline of Healthy China 2030 Plan. Applying highly sensitive methods to explore the presence of S. japonicum infection in its intermediate host will benefit to assess the endemicity or verify the transmission interruption of schistosomiasis accurately. The aim of this study was to access the presence of S. japonicum infection by a loop-mediated isothermal amplification (LAMP) method through a 5-year longitudinal study in five lake provinces along the Yangtze River. Methods: Based on previous epidemiological data, about 260 villages with potential transmission risk of schistosomiasis were selected from endemic counties in five lake provinces along the Yangtze River annually from 2015 to 2019. Snail surveys were conducted in selected villages by

systematic sampling method and/or environmental sampling method each year. All live snails collected from field were detected by microscopic dissection method, and then about one third of them were detected by LAMP method to assess the presence of S. japonicum infection with a single blind manner. The infection rate and nucleic acid positive rate of schistosomes in snails, as well as the indicators reflecting the snails' distribution were calculated and analyzed. Fisher's exact test was used to examine any change of positive rate of schistosomes in snails over time. **Results:** The 5-year survey covered 94,241 ha of environment with 33,897 ha of snail habitats detected accumulatively. Totally 145.3 ha new snail habitats and 524.4 ha re-emergent snail habitats were found during 2015-2019. The percentage of frames with snails decreased from 5.93% [45,152/761,492, 95% confidence intervals (CI): 5.88-5.98%] in 2015 to 5.25% (30,947/589,583, 95% CI: 5.19-5.31%) in 2019, while the mean density of living snails fluctuated but presented a downward trend generally from 0.20 snails/frame (155,622/761,492, 95% CI: 0.17-0.37) in 2015 to 0.13 snails/frame (76,144/589,583, 95% CI: 0.11-0.39) in 2019. A total of 555,393 live snails were collected, none of them was positive by dissection method. Totally 17 pooling snail samples were determined as positives by LAMP method among 8716 pooling samples with 174,822 of living snails, distributed in 12 villages of Hubei, Hunan, Jiangxi and Anhui provinces. The annual average positive rate was 0.41% (95% CI: 0.13-0.69%) in 2015, 0% in 2016, 0.36% (95% CI: 0.09-0.63%) in 2017, 0.05% (95% CI: 0-0.16%) in 2018, 0.05% (95% CI: 0-0.15%) in 2019, respectively, presenting a downward trend from 2015 to 2019 with statistical significance ($\chi^2=11.64$, $P<0.05$). **Conclusions:** The results suggest that S. japonicum infection still persisted in nature along the Yangtze River and traditional techniques might underestimate the prevalence of schistosomiasis in its intermediate hosts. Exploring and integrating molecular techniques into national surveillance programme could improve the sensitivity of surveillance system and provide guidance on taking actions against schistosomiasis.

## Schistosoma japonicum proteins that interact with the gynecophoral canal protein identified using a yeast two-hybrid system.

**Ren, Y., Li, M., Shi, Y., Liu, P., Wu, Q., Yang, Y., Zhang, L., Jin, Y.**
14-06-2022
*Exp Parasitol*
https://pubmed.ncbi.nlm.nih.gov/35714725

The large amount of schistosome eggs produced by mature female worms not only induce major pathological damage to the host but also lead to the transmission of schistosomiasis. Mature female schistosome worms need constant pairing contact with a male partner as male signaling is indispensable to female growth, development, and reproduction. The gynecophoral canal protein (GCP), a cell-surface glycoprotein, plays a potential role in the interaction between males and females and in stimulating female development and maturation. In this study, a yeast two-hybrid cDNA library of Schistosoma japonicum (Sj) parasites 18 days post-infection (dpi) was constructed; the Sjgcp gene was inserted into a pGBKT7-BD bait plasmid and used as a bait protein to screen for its molecular interactions using a yeast mating procedure. Twenty-four prey proteins that interacted with the SjGCP were selected after excluding false positives; the interactions between S.japonicum lethal giant larvae (SjLGL) and SjGCP, S.japonicum type V collagen (SjColV) and SjGCP, were verified by co-immunoprecipitation. The RNA interference against SjGCP, SjColV and SjGCP + SjColV led to severe underdevelopment of tegument in male worms and vitelline globules in female worms as well as reduced reproductive capacity of the females. Collectively, SjGCP and its interacting proteins may play pivotal roles in growth and development. The findings also suggested that SjGCP and its interacting protein partners might represent new candidate targets for drug development against schistosomiasis.

## Affordable artificial intelligence-based digital pathology for neglected tropical diseases: A proof-of-concept for the detection of soil-transmitted helminths and Schistosoma mansoni eggs in Kato-Katz stool thick smears.

**Ward, P., Dahlberg, P., Lagatie, O., Larsson, J., Tynong, A., Vlaminck, J., Zumpe, M., Ame, S., Ayana, M., Khieu, V., Mekonnen, Z., Odiere, M., Yohannes, T., Van Hoecke, S., Levecke, B., Stuyver, L.**
17-06-2022
*PLoS Negl Trop Dis*
https://doi.org/10.1371/journal.pntd.0010500

**Background:** With the World Health Organization's (WHO) publication of the 2021-2030 neglected tropical diseases (NTDs) roadmap, the current gap in global diagnostics became painfully apparent. Improving existing diagnostic standards with state-of-the-art technology and artificial intelligence has the potential to close this gap. **Methodology/Principal findings:** We prototyped an artificial intelligence-based digital pathology (AI-DP) device to explore automated scanning and detection of helminth eggs in stool-based specimens prepared with the Kato-Katz (KK) technique, the current diagnostic standard for diagnosing soil-transmitted helminths (STHs; Ascaris lumbricoides, Trichuris trichiura and hookworms) and Schistosoma mansoni (SCH) infections. First, we embedded a prototype whole slide imaging scanner into field studies in Cambodia, Ethiopia, Kenya and Tanzania. With the scanner, over 300 KK stool thick smears were scanned, resulting in total of 7,780 field-of-view (FOV) images containing 16,990 annotated helminth eggs (Ascaris: 8,600; Trichuris: 4,083; hookworms: 3,623; SCH: 684). Around 90% of the annotated eggs were used to train a deep learning-based object detection model. From an unseen test set of 752 FOV images containing 1,671 manually verified STH and SCH eggs (the remaining 10% of annotated eggs), our trained object detection model extracted and classified helminth eggs from co-infected FOV images in KK smears, achieving a weighted average precision (± standard deviation) of 94.9% ± 0.8% and a weighted average recall of 96.1% ± 2.1% across all four helminth egg species. **Conclusions/Significance:** We present a

proof-of-concept for an AI-DP device for automated scanning and detection of helminth eggs in KK stool thick smears. We identified obstacles that need to be addressed before the diagnostic performance can be evaluated against the target product profiles for both STH and SCH. Given that these obstacles are primarily associated with the required hardware and scanning methodology, opposed to the feasibility of artificial intelligence-based results, we are hopeful that this research can support the 2030 NTDs road map and eventually other poverty-related diseases for which microscopy is the diagnostic standard.

### Detection of schistosome infection in the invasive snail Melanoides tuberculata (Gastropoda: Thiaridae) by polymerase chain reaction from Plateau State, Nigeria: a novel turning point in disease epidemiology and control?

**Adubi, T., Otubanjo, O., Atalabi, T.**
17-06-2022
*Trans R Soc Trop Med Hyg*
https://pubmed.ncbi.nlm.nih.gov/35713978

Background: Melanoides tuberculata is a freshwater snail that serves as an intermediate host for 11 parasitic flukes. This study was conducted with the aim of identifying and screening the snail intermediate hosts in the study site for schistosomiasis using the molecular technique. Methods: DNA was extracted from the snails by the hexadecyl trimethyl ammonium bromide method and the Dra1 primer was used to amplify the Dra1 repeated sequence of Schistosoma haematobium. Results: The presence of schistosome DNA in M. tuberculata by polymerase chain reaction was confirmed. Conclusions: Our findings show that M. tuberculata is a potential intermediate host of schistosomes.

### NAD-catabolizing ectoenzymes of Schistosoma mansoni.

**Nation, C., Da'Dara, A., Skelly, P.**
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*Biochem J*
https://doi.org/10.1042/BCJ20210784

Infection with schistosomes (blood flukes) can result in the debilitating disease schistosomiasis. These parasites survive in their host for many years, and we hypothesize that proteins on their tegumental surface, interacting with the host microenvironment, facilitate longevity. One such ectoenzyme - the nucleotide pyrophosphatase/phosphodiesterase SmNPP5 can cleave ADP (to prevent platelet aggregation) and NAD (likely preventing Treg apoptosis). A second tegumental ectoenzyme, the glycohydrolase SmNACE, also catabolizes NAD. Here, we undertake a comparative biochemical characterization of these parasite ectoenzymes. Both are GPI-linked and exhibit different optimal pH ranges. While SmNPP5 requires divalent cations, SmNACE does not. The KM values of the two enzymes for NAD at physiological pH differ: SmNPP5, KM=340 µM±44; SmNACE, KM=49 µM±4. NAD cleavage by each enzyme yields different products. SmNPP5 cleaves NAD to form nicotinamide mononucleotide (NMN) and AMP, whereas SmNACE cleaves NAD to generate nicotinamide (NAM) and adenosine diphosphate ribose (ADPR). Each enzyme can process the other's reaction product. Thus, SmNACE cleaves NMN (to yield NAM and ribose phosphate) and SmNPP5 cleaves ADPR (yielding AMP and ribose phosphate). Metabolomic analysis of plasma containing adult worms supports the idea that these cleavage pathways are active in vivo. We hypothesize that a primary function of SmNPP5 is to cleave NAD to control host immune cell function and a primary function of SmNACE is to cleave NMN to generate the vital nutrient nicotinamide (vitamin B3) for convenient uptake by the worms. Chemical inhibition of one or both ectoenzymes could upset worm metabolism and control schistosome infection.

### Infection History and Current Coinfection With Schistosoma mansoni Decreases Plasmodium Species Intensities in Preschool Children in Uganda.

**McDowell, D., Hurt, L., Kabatereine, N., Stothard, J., Lello, J.**
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*J Infect Dis*
https://doi.org/10.1093/infdis/jiac072

Malaria-schistosomiasis coinfections are common in sub-Saharan Africa but studies present equivocal results regarding the interspecific relationships between these parasites. Through mixed-model analyses of a dataset of Ugandan preschool children, we explore how current coinfection and prior infection with either Schistosoma mansoni or Plasmodium species alter subsequent Plasmodium intensity, Plasmodium risk, and S mansoni risk. Coinfection and prior infections with S mansoni were associated with reduced Plasmodium intensity, moderated by prior Plasmodium infections, wealth, and host age. Future work should assess whether these interactions impact host health and parasite control efficacy in this vulnerable age group.

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

### Human hookworms from Argentina: Differential diagnosis of Necator americanus and Ancylostoma duodenale in endemic populations from Buenos Aires and Misiones.

**Servián, A., Repetto, S., Lorena Zonta, M., Navone, G.**
17-06-2022
*Rev Argent Microbiol*
https://pubmed.ncbi.nlm.nih.gov/35725664

Hookworm infection is endemic in many countries throughout

the world; however, the information about the prevalence of each species, Necatoramericanus and Ancylostomaduodenale, is inaccurate in many South American countries. We aimed to determine the prevalence of human hookworm species by combining the results of both microscopy and PCR among endemic populations in Argentina, represented by natives and immigrants. A total of 140 serial fecal specimens were obtained from natives in the province of Misiones and an immigrant community living in the province of Buenos Aires. Samples were examined using the formalin-ethyl acetate concentration technique (FECT) and one flotation technique (screening tests) and specific PCRs for N. americanus and A. duodenale. We characterized samples containing N. americanus by sequencing a fragment of the cytochrome b gene. The observed hookworm prevalence as assessed by the screening tests and PCR were 24.3% and 32.8%, respectively. PCR positive samples were identified as N. americanus. PCR had 100% sensitivity compared with 73.9% of screening tests. A total of 12 samples from individuals with hookworm-infected household members were positive only by PCR. N. americanus sequences showed 90.5% identity, being more similar to each other than to any of the sequences obtained from GenBank. This is the first study that provides molecular data and characterization of N. americanus in Argentina. The complementary use of FECT and one flotation technique to screen hookworm infections, followed by PCR to differentiate the species contribute to produce better prevalence estimates.

## Affordable artificial intelligence-based digital pathology for neglected tropical diseases: A proof-of-concept for the detection of soil-transmitted helminths and Schistosoma mansoni eggs in Kato-Katz stool thick smears.

**Ward, P., Dahlberg, P., Lagatie, O., Larsson, J., Tynong, A., Vlaminck, J., Zumpe, M., Ame, S., Ayana, M., Khieu, V., Mekonnen, Z., Odiere, M., Yohannes, T., Van Hoecke, S., Levecke, B., Stuyver, L.**
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*PLoS Negl Trop Dis*
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Background: With the World Health Organization's (WHO) publication of the 2021-2030 neglected tropical diseases (NTDs) roadmap, the current gap in global diagnostics became painfully apparent. Improving existing diagnostic standards with state-of-the-art technology and artificial intelligence has the potential to close this gap. Methodology/Principal findings: We prototyped an artificial intelligence-based digital pathology (AI-DP) device to explore automated scanning and detection of helminth eggs in stool-based specimens prepared with the Kato-Katz (KK) technique, the current diagnostic standard for diagnosing soil-transmitted helminths (STHs; Ascaris lumbricoides, Trichuris trichiura and hookworms) and Schistosoma mansoni (SCH) infections. First, we embedded a prototype whole slide imaging scanner into field studies in Cambodia, Ethiopia, Kenya and Tanzania. With the scanner, over 300 KK stool thick smears were scanned, resulting in total of 7,780 field-of-view (FOV) images containing 16,990 annotated helminth eggs (Ascaris: 8,600; Trichuris: 4,083; hookworms: 3,623; SCH: 684). Around 90% of the annotated eggs were used to train a deep learning-based object detection model. From an unseen test set of 752 FOV images containing 1,671 manually verified STH and SCH eggs (the remaining 10% of annotated eggs), our trained object detection model extracted and classified helminth eggs from co-infected FOV images in KK smears, achieving a weighted average precision (± standard deviation) of 94.9% ± 0.8% and a weighted average recall of 96.1% ± 2.1% across all four helminth egg species. Conclusions/Significance: We present a proof-of-concept for an AI-DP device for automated scanning and detection of helminth eggs in KK stool thick smears. We identified obstacles that need to be addressed before the diagnostic performance can be evaluated against the target product profiles for both STH and SCH. Given that these obstacles are primarily associated with the required hardware and scanning methodology, opposed to the feasibility of artificial intelligence-based results, we are hopeful that this research can support the 2030 NTDs road map and eventually other poverty-related diseases for which microscopy is the diagnostic standard.

## Development of allele-specific PCR methodology (AS-PCR) to screening A. lumbricoides and A. suum.

**Dos Santos, T., Furtado, L., de Carvalho Araujo, A., da Silva Medeiros, C., Germano, P., de Oliveira, V., Rabelo, E.**
17-06-2022
*Parasitol Res*
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Ascaris lumbricoides and Ascaris suum are described as helminths that infect humans and pigs, respectively. It is estimated that infection by A. lumbricoides affects about 447 million individuals living in tropical regions of developing countries. However, there is an increasing number of cases of human ascariasis in countries with no recent history of autochthonous infection by A. lumbricoides. In these places, pigs have been incriminated as the main source of human infection. Conventional parasitological diagnosis does not allow species-specific identification, and the real epidemiological scenario of human and swine ascariasis is still uncertain. Therefore, this work presents the application of a species-specific molecular diagnosis, based on the allele-specific PCR methodology (AS-PCR), using the Internal Transcript Space 1 (ITS-1) of the ribosomal DNA, as a target for differentiating between the two species, using DNA obtained from eggs. To validate the methodology, stool samples positive for Ascaris spp, were obtained from 68 humans from seven Brazilian states and from six pigs from the state of Minas Gerais. All samples obtained from humans were genotyped as A. lumbricoides and all samples obtained from swine were genotyped as A. suum. These results are in agreement with the literature, which demonstrates that in most endemic regions, transmission cycles are separate. Therefore, the execution of this work allowed the availability of a useful methodology for the differential diagnosis of the

species, which may contribute to the characterization of the real epidemiological profile of human and swine ascariasis, and to the implementation of future control strategies.

## GALE

### Scabies revisited in the COVID-19 era.

**Trave, I., Muracchioli, A., Cozzani, E., Parodi, A.**
20-06-2022
*J Eur Acad Dermatol Venereol*
https://doi.org/10.1111/jdv.18335

### Localized crusted scabies over the engrafted skin: Report of two cases.

**Ahmed, G., Anju George, C., Rahim, J., Ganguly, S.**
17-06-2022
*J Cosmet Dermatol*
https://doi.org/10.1111/jocd.15164

### Prevalence and determinants of scabies among school-age children in Central Armachiho district, Northwest, Ethiopia.

**Misganaw, B., Nigatu, S., Gebrie, G., Kibret, A.**
14-06-2022
*PLoS One*
https://doi.org/10.1371/journal.pone.0269918

Background: Scabies is a major global public health issue that might affect people from all socioeconomic levels. Globally, scabies affects more than 200 million people at any time. It remains one of the commonest skin diseases seen in developing countries including Ethiopia. Therefore, this study aimed to assess the prevalence and determinants of scabies among school-age children in Central Armachiho district, Northwest Ethiopia. Methods: A community-based cross-sectional study was conducted from August to September 2020. A multi-stage sampling technique was used to select 850 study populations. Data was checked for its completeness, coded, and entered by using EPI-INFO version 7 and exported to the SPSS version 20 for analysis. A Binary logistic regression model was fitted to identify the determinants of scabies. Crude odds ratio (COR) and adjusted odds ratio (AOR) with 95% CI were used as measurements for the associations. P-values <0.005 were considered significant. Result: Prevalence of scabies among the 850 participants studied was 10.82% (95% CI: 8.7-12.9). Contact history with confirmed scabies patient (AOR = 5.28,95% CI: 2.96-9.44), child not attending school (AOR = 3.08, 95% CI;1.45-6.54), rarely changing clothes (AOR = 2.43,95% CI: 1.27-4.62), sleeping on the floor (AOR = 4.11, 95% CI:1.95-8.67), bed sharing; (AOR = 3.38, 95% CI:2.86-6.15), rarely washing cloth: (AOR = 5.08,95% CI:2.75-9.36), living with internally displaced people; (AOR,95% CI: 3.47 (1.30-9.24) and using only water to wash hands; (AOR = 3.18,95% CI:1.74-5.80) had a statistically significant association with scabies infestation among school-age children. Conclusion: The current study found nearly one out of ten school-age children had scabies. Not attended school, contact history with confirmed scabies patient, not washing cloth, infrequent changing clothes, bedding sharing, sleeping on the floor, living with internally displaced people, and only using water for handwashing practice were the independent predictors for the occurrence of scabies. Health education better to given to the parents or caregivers about the washing of clothing, changing clothes at least once per week, and avoid physical contact with known scabies cases.

## MORSURES DE SERPENT

### Protective effects of novel diazepinone derivatives in snake venom induced sterile inflammation in experimental animals.

**Alam, M., Quasimi, H., Kumar, A., Alam, A., Bhagat, S., Alam, M., Khan, G., Dhulap, A., Ahmad Ansari, M.**
18-06-2022
*Eur J Pharmacol*
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Snake envenomation leads to the formation of damage-associated molecular patterns (DAMPs), which are mediated by endogenous intracellular molecules. These are recognized by pattern-recognition receptors (PRRs) and can induce sterile inflammation. Aims: In the present study, we aim at understanding the mechanisms involved in DAMPs induced sterile inflammation to unravel the novel therapeutic strategies for treating snake bites. The potential of benzodiazepinone derivatives to act against snake venom induced inflammation has been explored in the present investigation. Main methods: Three compounds VA 17, VA 43 and PA 03 were taken from our library of synthetic compounds. Oxidative stress markers such as lipid peroxidation, superoxide and nitric oxide were measured along with the analysis of DAMPs (IL6, HMGB1, vWF, S100b and HSP70). These compounds have been docked using molecular docking against the snake venom $PLA_2$ structure (PDB code: 1OXL). Key findings: The compounds have been found to effectively neutralize viper and cobra venoms induced lethal activity both ex vivo and in vivo. The compounds have also neutralized the viper venom induced hemorrhagic, coagulant, anticoagulant reactions as well as inflammation. The fold of protection have always been found to be higher in case of ex vivo than in in vivo. These compounds have neutralized the venom induced DAMPs as exhibited by IL6, HMGB1, vWF, S100b and HSP70. The fold of neutralization is found to be higher in VA 43. Significance: The identified compounds could be used as potential candidates for developing treatment of snakebites in areas where antiserums are not yet available.

## Upper Extremity Crotalid Envenomation: A Review of Incidence and Recent Trends in Management of Snakebites.

**Razavi, S., Stewart, C., Nogee, D., Geller, R., Seiler, J.**
17-06-2022
*J Hand Surg Am*
https://pubmed.ncbi.nlm.nih.gov/35725686

**Purpose:** The goal of this study was to evaluate the recent trends in the management of upper extremity Crotalid envenomation in the state of Georgia, United States. **Methods:** A retrospective review of the Georgia Poison Center database looking at the reported snakebites to the upper extremity between 2015 and 2020 was performed. Patient demographics, timing and location of injury, severity of envenomation, treatment, including use of antivenin and surgical intervention, and reported complications related to the use of antivenin was extracted. **Results:** A retrospective review of snakebites between 2015 and 2020 showed 2408 snakebite cases with a mean patient age of 37.4 years. Males incurred 62.8% of all bites. The highest incidence was in summer 52.5%, and between the hours of 5 PM to midnight 57.2%. Overall, 1010 (41.9%) of all bites were categorized as venomous snakebites (55.6% copperhead, 20% rattlesnake, 2.4% cottonmouth, and 22% miscellaneous [including 3 Elapid envenomations] or unidentified. The total number of venomous bites to the upper extremity was 575 (56.9%) and 567 patients received antivenin. Envenomation severity was mild in 29%, moderate in 45%, severe in 10%, and undetermined in 16% of cases. Crotalidae polyvalent immune Fab (Ovine) was the main antivenin used, with overall mean initial therapy dose of 6.2 vials and 59% of patients receiving maintenance therapy. Three patients (0.5%) had a severe anaphylactic reaction to antivenin requiring cessation of therapy. Seven patients had acute compartment syndrome of the upper extremity requiring fasciotomy (3 copperhead, 2 rattlesnake, and 2 unidentified). There was no reported mortality during this period. **Conclusions:** Hand surgeons should be familiar with the management of upper extremity Crotalid envenomation. Antivenin remains the main treatment for symptomatic patients. Crotalid snakebites rarely require operative intervention. Level IV, Prognostic.

## Traditional remedies and other characteristics among human snakebite survivors in Baringo county, Kenya, 2010-2020: a case series.

**Kung'u, P., Chweya, R., Gachohi, J.**
20-06-2022
*Int Health*
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**Background:** Seeking traditional remedies following snakebites leads to avoidable deaths in rural settings in developing countries. **Methods:** In this case series study, we identified and recruited 169 snakebite survivors in Baringo county, a hard-to-reach region in northwestern Kenya, who experienced snakebites from 2010 to 2020 using a snowballing technique. We explored associations between traditional and hospital care in managing snakebites and other characteristics. $\chi 2$ tests assessed these categorical differences. **Results:** Fifty-four (33%) of the survivors used traditional remedies to manage snakebites. The majority (56%) were men and aged >18 y (72%); 59% had low education levels and income. They sourced water from rivers or lakes (93%) and used charcoal as an energy source (74%). These survivors (>67%) resided in households practicing free-range and stall-feeding animal husbandry systems and in houses with thatch roofing or an earthen floor structure. Also, >62% reported muscle tremors, fever and chills, while 80% visited health facilities for further treatment. **Conclusion:** Community sensitization covering the risks of non-effective remedies and escalation of training to traditional healers could improve the speed of referrals in hard-to-reach snakebite hotspots. Medical anthropology studies could explore the enablers of continued use of traditional remedies in snakebite management in rural communities.