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REVIEW ARTICLE

# Visceral leishmaniasis in the COVID-19 pandemic era

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Visceral l eishmaniasis (VL), also known as kala-azar, had once been targeted for elimination in 2020, which now has been shifted to 2030. The year 2020 was also the year in which the world was gripped by the coronavirus disease 2019 (COVID-19) pandemic. This review sheds light on the impact of COVID-19 on VL elimination programmes and the increasing incidences of COVID-19/VL cases. Lockdowns were imposed worldwide that led to the suspension of surveys, active case finding and mass drug administration, which are important activities to manage neglected tropical diseases. Healthcare machinery was redirected to control the pandemic and acute resource shortages were seen. Budget cuts from funding agencies and donors also came as a severe blow. Priority changes for manufacturers of drugs and diagnostic kits have also exacerbated the situation. Cases where patients were co-infected with VL and COVID-19 were reported across various settings and in people of various age groups, posing unprecedented challenges in diagnosis and treatment. Concerted efforts from all stakeholders are required to understand and deal with the impact that this pandemic has had on VL.

**Keywords:** elimination programme, COVID-19, co-infection, neglected tropical disease, visceral leishmaniasis

## Introduction

The havoc that the coronavirus disease 2019 (COVID-19) pandemic has caused needs no separate introduction. In this review we present the upheaval it has caused in relation to visceral leishmaniasis (VL). VL, or kala-azar, is a neglected tropical disease (NTD) that was targeted for elimination as a public health problem (EPHP) in the year 2020. But due to several factors, the target has been moved to the year 2030. Its elimination comes under Sustainable Development Goal 3. It is the second largest parasitic killer after malaria and the fatal disease is caused by members of genus *Leishmania*.[1–3]

Along with lockdowns being imposed in different parts of the world due to the pandemic, NTD elimination programmes were also stalled, as the World Health Organization (WHO) called for postponing active case finding, mass drug administration and surveys for several NTDs.[4]

Liposomal amphotericin B is the most extensively used treatment option for VL, but its manufacturer and donor have redirected their resources towards other priorities and we are looking at an impending global shortage of the first-line treatment for VL. Even the diagnosis of VL using rapid diagnostic tests is going to be a hurdle, as the only manufacturer ceased production of these tests in 2022 due to modifications in regulations.[1]

A significant decline in case consultations was noted for VL in Brazil in 2020. In the same setting, clinical visits for tegumentary leishmaniasis increased by 57% compared with the pre-pandemic era (2017–2019).[5] Several incidences of co-infection of VL and COVID-19 were seen. People of diverse age groups across different countries were involved. Many of the patients recovered, but others succumbed to this co-infection. Immunosuppressed patients had worse clinical outcomes in cases of co-infections. Diagnosis of this co-infection was challenging in several instances. However, timely diagnosis and initiation of treatment led to better clinical outcomes for these patients.[6–11]

Here we attempt to understand the impacts and challenges that this pandemic has presented to the VL scenario worldwide using currently available literature and data.

## Elimination programme interruption

It was well-understood that the progress made on NTDs would suffer a setback as a consequence of interruptions to elimination programmes. To determine the impact of the interruptions for VL, a deterministic transmission model was used.[12–15] Indoor residual spraying of insecticides and active case detection intervention strategies that were adopted to meet the 2020 and 2030 elimination targets across the Indian subcontinent (ISC) were stalled. It was forecasted that an upsurge in VL incidence could be expected but this interruption would not undo all the prior achievements made.[16]

The pandemic placed a huge burden on the healthcare system and adversely impacted dealing with VL and other NTDs.[17,18]

Similar to other parts of the world, the control programme was interrupted in India. On modelling the impact of the interruptions, it was estimated that a 1-y interruption would result in a setback of 0–7 y in reaching elimination. Other factors influencing this outcome would be the endemicity of the area and the stage at which the control programme was stalled. The areas that had reached the 'elimination' target before this interruption could be at risk of an increase in cases and could lose the achievement made. Further, a surge in VL cases was anticipated across all settings.[19]

Also, delays in case detection may prove to be a better yardstick than the number of cases detected in estimating the influence of interruptions. The detection of post–kala-azar dermal leishmaniasis (PKDL) could also be hampered due to the pandemic. While modelling the impacts, many actual factors that could have shaped the situation were not accounted for, including the huge migration of people from cities to villages at the beginning of the lockdown, which resulted in many susceptible people moving into endemic settings and also infected people moving to non-endemic settings. The expected effects vary from village to village.[19] Some places may not see changes in VL cases, while other settings might experience outbreaks, as seen in Korsa village in Bihar.[20] This interruption may potentially hamper and postpone the WHO's VL elimination goal of 2030.[19]

The interruptions in elimination programmes may have wide-ranging impacts over diverse VL-endemic settings, thus re-initiation of these programmes is important. The elimination programme may be further strengthened by its integration with surveillance and mitigation mechanisms for COVID-19.[21–23]

## Budget cuts and shortage of resources for diagnosis and treatment

Funding agencies have now prioritized COVID-19, which has led to funds shortages for NTDs like VL.[24] With a budget cut in the UK in November 2020, a €4 billion international fund was lost. This has resulted in termination of a programme that funded life-saving medications for VL worldwide. Additionally, in April 2021, the UK's Foreign Commonwealth and Development Office instituted a 90% reduction in the funding of NTD programmes. Funds from the UK for global leishmaniasis response have been reduced, which will lead to untimely stopping of the Accelerating Sustainable Control and Elimination of Neglected Tropical Disease (ASCEND) Programme. It had been contributing towards procurement of lifesaving medications. In the absence of any other funding body intervening, shortages of drugs for treatment and diagnostic tests are very likely. It will also increase the chances of probable VL transmissions, infections and outbreaks. Countries such as Ethiopia, South Sudan and Sudan were heavily dependent on this flagship ASCEND programme.[1,2,25–27]

Due to the COVID-19 situation, development of diagnostic tests in the pre-qualification pipeline for several NTDs, including leishmaniasis, were delayed. Thus for leishmaniasis, a fresh timeline is required.[2] In May 2022, the only highly sensitive rapid diagnostic test suitable for VL diagnosis in East Africa (IT-Leish; Bio-Rad Laboratories, Hercules, CA, USA) was discontinued by the manufacturer. This was due to the revision of European regulations for *in vitro* diagnostics. To comply with the new guidelines, time and monetary investment would be needed from the manufacturer. At present, there are no other manufacturers of this rapid diagnostic test.[1] The WHO's Diagnostics Technical Advisory Group prioritizes rapid diagnostic tests and leishmania skin tests as important factors to achieve the 2030 goal and their absence could be a threat to the WHO's 2030 target to eliminate VL as a public health concern.[28]

During the pandemic, liposomal amphotericin B was used to treat mucormycosis in COVID-19 patients, leading to a worldwide shortage as manufacturers struggled to meet demand. Gilead, the lead manufacturer of this drug, is now producing remdesivir in place of liposomal amphotericin B (AmBisome). The manufacturers of the generic form are not properly qualified as per international standards, which limits its procurement.[1,26,29]

## COVID-19 and VL co-infection: challenges in diagnosis and treatment

As the COVID-19 pandemic spreads worldwide, in a few cases it has co-occurred with VL. To date, there have been six reported cases of COVID-19–VL co-infection. Some patients survived the co-infection and it was fatal in others.

The first case of COVID-19–VL co-infection was reported in July 2020 from Italy, in a 79-year-old male. The patient had fever, pancytopenia, weight loss and asthenia. Comorbidities such as hypertension, previous history of myocardial infarction and myasthenia gravis were present. Serological investigations and bone marrow biopsy confirmed the diagnosis of VL. Treatment was started with liposomal amphotericin B and meanwhile the patient developed hospital-acquired COVID-19 infection. Antiviral therapy of darunavir and ritonavir was administrated but the condition of the patient continued to deteriorate. The patient developed ground-glass opacities in the chest and interstitial pneumonia, followed by severe thrombocytopenia and sepsis. To deal with this, dexamethasone, piperacillin-tazobactam and vancomycin, along with supportive treatment (transfusions of plasma, red blood cells and platelets supported by granulocyte colony stimulating factor), were given. Unfortunately, due to failure of multiple organs, the patient passed away. This was an exceptional case where the patient's comorbidities and immunosuppression led to acquisition of two fatal infections.[6]

Another co-infection case was reported later in 2020 in a young (age 29 months) male child in Iran. This patient had a history of fever for 2 months and was referred to a tertiary care hospital. The child was found to be COVID-19 positive, had pleural effusions in his lungs, splenomegaly and pancytopenia. It was first diagnosed as hemophagocytic lymphohistiocytosis, which is a rare disease, and treatment was started with prednisolone. Since the child also had an atypical lymphocyte count, a bone marrow aspiration was done that showed Leishman–Donovan bodies. Following this observation, amphotericin B was administered and the condition of the patient improved. In a normal situation, the symptoms would have clearly led to the clinical diagnosis of leishmaniasis. But the presence of COVID-19 infection led to confusion. The misdiagnosis adds to the problem, as most

VL cases are asymptomatic and the symptoms can be vague in some patients. VL usually occurs in tropical countries where other infectious diseases are also rampant. Therefore, it is important to be aware of the differential diagnoses and rule out other diseases in a stepwise manner. Even during a pandemic, it is crucial to correctly diagnose this fatal disease.[7]

Another case of co-occurrence of both the infections was reported from Ethiopia in an 18-year-old male. The patient had recurring fever (with chills and rigors) for 2 weeks and experienced a loss of appetite, weight loss, fatigue, loose stools and cramps in the lower abdomen. This patient did not respond to anti-malarial therapy along with ceftriaxone antibiotic therapy. However, his COVID-19 test was positive and he showed pancytopenia, hyperbilirubinemia, lymphadenopathy and splenomegaly. While he was being treated for the viral infection, his condition continued to deteriorate and he developed septic shock, liver dysfunction and bleeding. Since the patient had some symptoms related to VL and a travel history to a leishmania-endemic area, serological tests and bone marrow aspiration were done. VL was diagnosed. The only available treatment for VL accessible to them was sodium stibogluconate and the treatment was started. Unfortunately, the patient's septicaemia worsened and he had liver haemorrhage, leading to his death.[8]

In 2021, a co-infection case was reported in a 28-year-old male who was admitted to a hospital for pneumonia caused by the COVID-19 infection. In addition to headache, mild fever and ground-glass opacities in the lungs, the patient had pancytopenia and hepatosplenomegaly. Bone marrow aspirate confirmed the VL diagnosis. Amphotericin B was given to the patient intravenously and he responded to the treatment. Here, prompt diagnosis and treatment was done.[10]

In Athens, Greece, a 22-year-old female was reported to have the co-infection. She was an immigrant who arrived 3 y earlier from Afghanistan. The patient was brought to a healthcare centre due to complaints of fever and diarrhoea. She was found to be COVID-19 positive. Additionally, she also had lymphadenopathy, hepatosplenomegaly and pancytopenia. Serological tests were positive for anti-leishmanial antibodies. Amastigotes of *Leishmania* were present in the bone marrow biopsy. *Leishmania infantum* was identified as the causative organism using restriction fragment length polymorphism and genus-specific polymerase chain reaction. For the COVID-19 infection treatment, the patient was prescribed dexamethasone and enoxaparin. Remdesivir doses were stopped due to the elevation of aspartate aminotransferase and alanine aminotransferase. Liposomal amphotericin B was used to treat VL. After improvement in her clinical condition, the patient was discharged. The authors hypothesized that the COVID-19 infection might have reactivated the latent or asymptomatic infection in the patient. The association between these two infections needs further exploration to devise better treatments and controls for this co-infection.[9]

Another co-infection case was reported in a 41-year-old immunosuppressed female who resided in a VL-endemic region. She had been a rheumatoid arthritis patient for 20 y and was being treated with methotrexate and leflunomide. The patient developed lesions on her skin and oral mucosa and abdominal pain and was diagnosed with pemphigus vulgaris. Corticosteroids at a high dose were prescribed for 60 d. Her condition further deteriorated, she developed jaundice and her abdominal volume increased. She was hospitalized at around day 50 of treatment with corticosteroids. She was found to have ascites, hepatosplenomegaly, an altered hepatic profile, thrombocytopenia and anaemia. She also started bleeding from her vaginal and oral cavities, as her abdominal volume was high. She was then transferred to another hospital. Several other observations were made, including ground-glass appearance, and she was positive for COVID-19. Free amastigotes were visible in the blood smear. VL was confirmed by a rapid test and *L. (L.) infantum chagasi* was identified as the causative species. The patient's condition worsened and she passed away 2 d after hospitalization. This is also the first report where free amastigotes and amastigotes inside monocytes and neutrophils were observed for the diagnosis of human American VL. The case report also mentions that due to the delayed diagnosis of VL, no treatment could be initiated.[11]

## COVID-19, now a comorbidity for VL

COVID-19 can also be an aggravating factor for VL. In the 18-year-old patient discussed previously, it is possible that the VL had been asymptomatic, as the parasite load was low. Also, treatment of the COVID-19 infection with corticosteroids may have led to reactivation of VL.[8] The symptoms of COVID-19 overlap with other infectious diseases. There are no clear-cut features that can help differentiate COVID-19 from other contagions.[30] In areas endemic for VL, the co-infection pathogenesis could also be due to the fact that VL patients may have less-effective immune function.[31] Additionally, when COVID-19 patients who reside in endemic areas or have lived there in past show symptoms such as fever and cytopenia and are being treated using immunosuppressants, they should be monitored for leishmaniasis.[24] Proper and timely diagnosis of this co-infection could be pivotal to prevent fatalities.[7,9,10]

## Possibility of using the advancements made during COVID-19 for VL in diagnostics, surveillance and drugs

In most areas in which VL and other NTDs have a high prevalence, COVID-19 control measures have been ineffective. Thus there are more chances for co-infection. Cases of co-infection should be highlighted so that their pathology, clinical implications and epidemiology can be better understood. This kind of data is crucial for healthcare providers and government agencies to formulate and update their policies for control and surveillance.[22]

It is imperative to emphasize the rekindling of elimination programmes and mitigation strategies. In high-transmission areas, considerable impact on the mortality and morbidity of VL can be expected.[19] For VL, delays and interruptions in active and passive case finding will need special attention. Several models have been used to predict the impact of interruption and need for mitigation strategies.[32] Vector control and active case detection should be performed and, while implementing these strategies, high-transmission areas should be given priority. It is necessary to resurvey the VL-affected areas to validate the

predictions made by the models. Since the COVID-19 pandemic has brought a lot of improvements in surveillance, VL could potentially benefit from integration of these surveillance programmes. Strengthening of efforts from the WHO, donors and researchers is required in response to COVID-19-induced setbacks.[21]

## What impact is expected on VL?

For VL in the ISC, the attack phase of the elimination programme should be restarted and extended as a potential strategy suggested by the WHO in a model-based analysis to predict the impact of the pandemic. Model based analysis revealed that the highly endemic settings where the control programmes have been going on for 5–8 y will be the worst hit. If there is a 12-month interruption and if steps to mitigate the situation are not taken, it will result in a delay of 7–8 y. Also, an increase in the number of cases can be expected. If the interruption is for 6 months in a medium-endemic setting, there could be a delay of 1 y to reach the EPHP target.[23] To mitigate the situation, if the attack phase is extended, the delay in reaching the EPHP target can be reduced by 4.5 y. This would also mean a reduction in the fresh cases of VL.[21] For endemic areas, the WHO also suggests that active case detection should be done at least once a year.[33,34] It should also be considered that a decrease in VL cases may be seen during this period while the incidence of VL may actually be increasing.[23] The VL elimination programme in India has been reinitiated after the interruption due to the COVID-19 pandemic, however, its effects are yet to be understood.[35]

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