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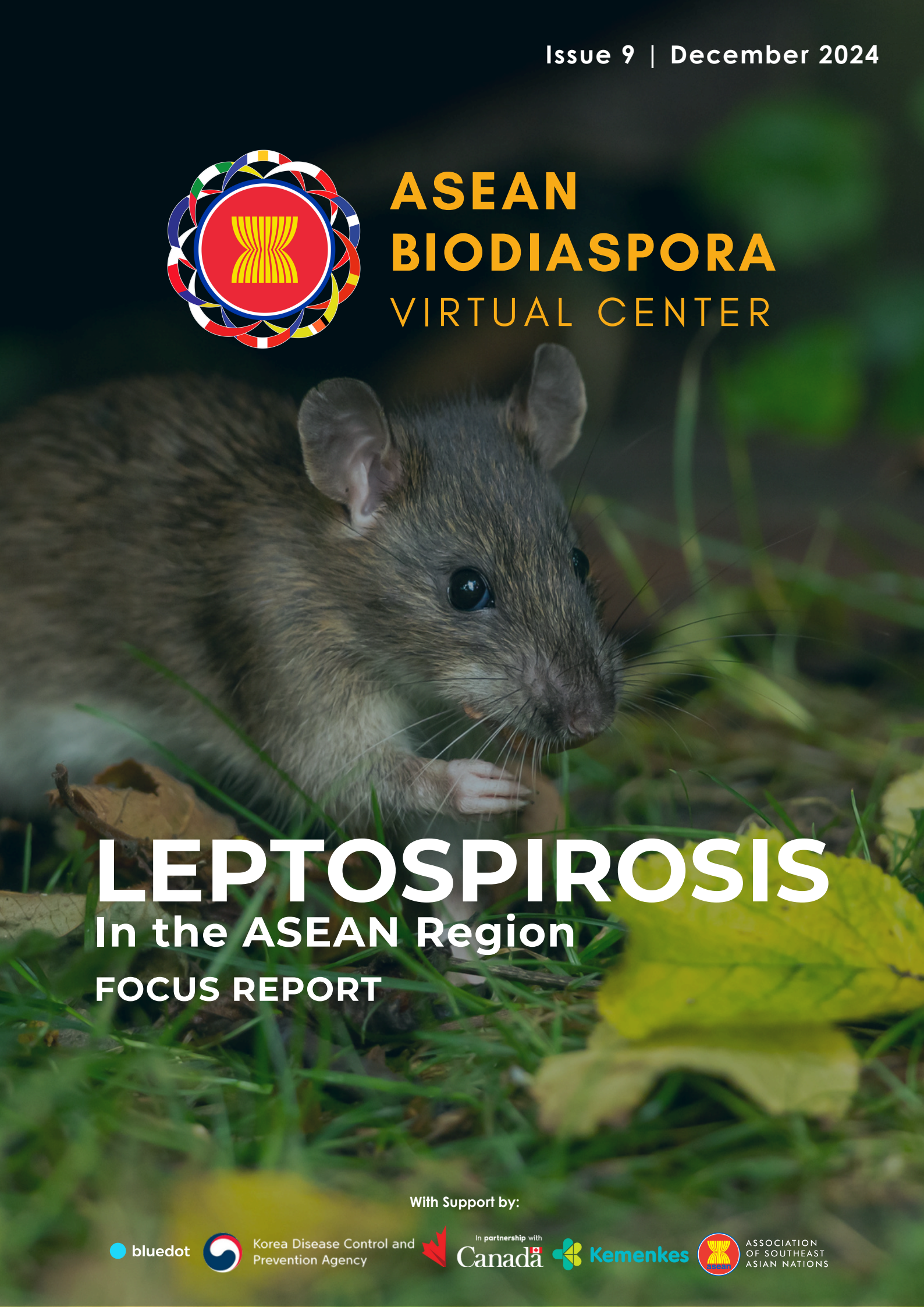
ASEAN BIODIASPORA VIRTUAL CENTER



LEPTOSPIROSIS

In the ASEAN Region

FOCUS REPORT

With Support by:

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Korea Disease Control and Prevention Agency

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Kemenkes

ASSOCIATION OF SOUTHEAST ASIAN NATIONS

ASEAN BIODIASPORA VIRTUAL CENTER

Editorial

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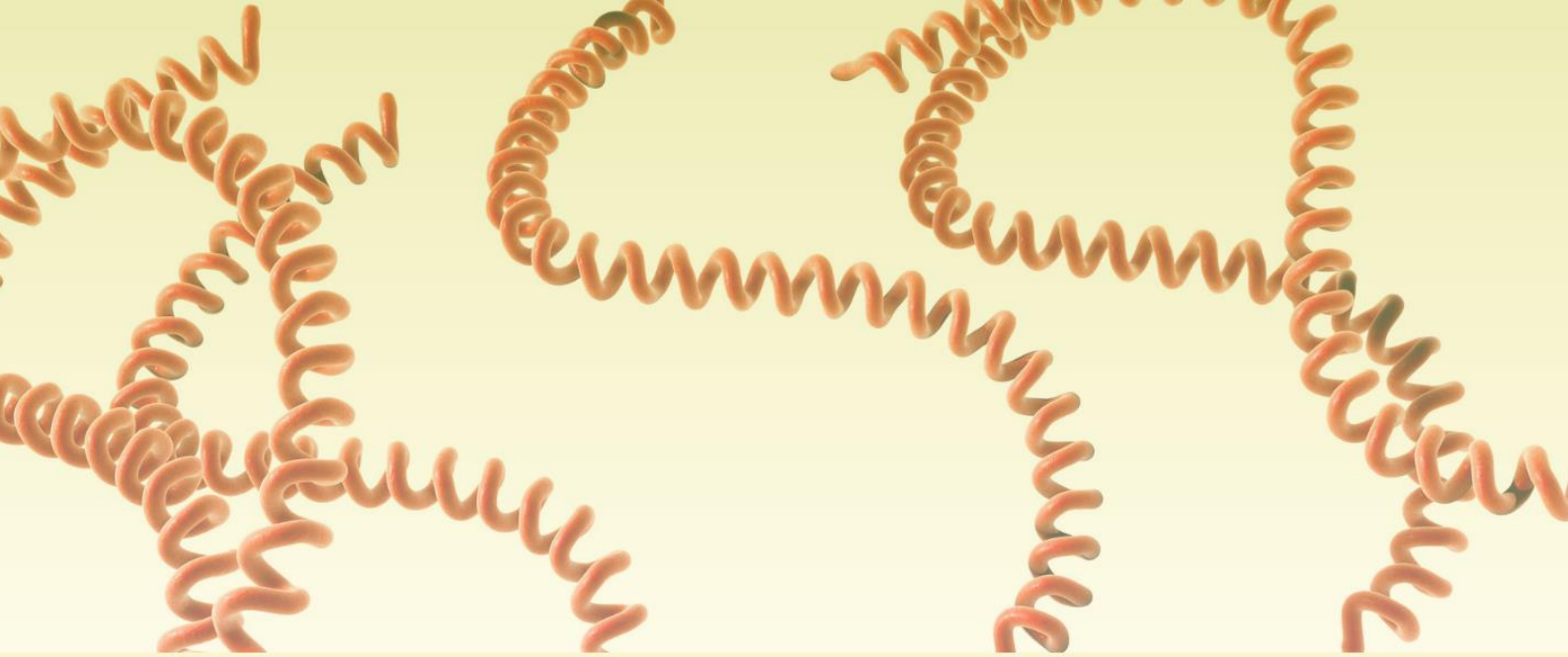
LEPTOSPIROSIS FOCUS REPORT



1 Introduction

Leptospirosis, a zoonotic disease caused by *Leptospira* bacteria, is a major global health threat, particularly in tropical and subtropical regions. Transmitted through contact with contaminated water, soil or animal tissue, it disproportionately affects populations in high-risk environments. The disease is an ongoing global public health challenge, with climate change and extreme weather events such as floods accelerating its spread and contributing to outbreaks in Asia, Latin America and the Pacific.

This report provides an overview of leptospirosis, including its transmission, symptoms, and treatment, as well as current data on incidence and mortality. It also focuses on the regional situation within ASEAN, analysing the disease's impact and the region's collective efforts to combat it through surveillance, rapid response, and public health initiatives. Through this focus, the aim of the report is to elucidate the critical role of prevention and preparedness in reducing leptospirosis's burden across vulnerable populations.

2 Methods

This report employs a comprehensive literature review to explore the global landscape of leptospirosis, with a particular focus on the ASEAN region. The data was collated from established databases, including PubMed, Embase and Scopus, using keywords pertinent to leptospirosis and the ASEAN region. Furthermore, data on the incidence of disease, diagnostic criteria, preventative measures and policy strategies were collated from official reports and news sources on leptospirosis cases. This comprehensive approach enabled a detailed analysis of the current trends, patterns, and challenges associated with the management of leptospirosis within the ASEAN region.

3 Case Definition and Clinical Features

Case Definition

Leptospirosis is a communicable disease affecting both animals and humans, caused by infection with Leptospira, a genus in the order Spirochaetes and the family Leptospiraceae. The typical dimensions of these bacteria are 0.1 μm in diameter and 6 to 20 μm in length. The Leptospira genus is characterized by flexible, spiral-shaped cells with distinctive hooked ends and two internal flagella that allow motility to facilitate migration across tissue barriers. The bacterial cell wall contains lipopolysaccharide (LPS), similar to other Gram-negative bacteria. While the heritability of leptospirosis remains unclear, structural variations in LPS contribute to the identification of over 200 serovars within Leptospira (Haake, et al., 2021; Verma, et al., 2020).

Leptospires exhibit relatively slow growth in both liquid and solid media. The warm, humid climate of tropical and subtropical regions creates favorable conditions for Leptospira to persist in the environment for long periods (Benacer et al., 2013). Optimal growth temperatures range from 28 and 30°C in media supplemented with long-chain fatty acids, vitamins B1 and B12, and ammonium salts (Evangelista and Coburn, 2011). Certain pathogenic strains, such as L. interrogans, however, can survive in low-nutrient environments, such as moist soil and fresh water for long periods, with salt concentration, pH and viscosity as critical factors. In contrast, L. borgpetersenii does not survive outside a host, and genomic analyses indicate that loss of essential genes for environmental survival restricts its transmission to direct host-to-host contact (Trueba et al., 2003; Bulach, et al., 2006).

Clinically, leptospires are classified as pathogenic (parasitic and infectious) or non-pathogenic (saprophytic and non-infectious). Pathogenic species, which cause disease, include L. interrogans, L. borgpetersenii, and L. kirschneri, totaling over 250 serovars. Non-pathogenic species, like L. biflexa and L. meyeri, occur freely in nature and encompass more than 60 serovars (Levett, 2001). Saprophytic species are naturally present in environmental water and soil and do not usually cause disease in healthy individuals. Leptospirosis occurs when pathogenic species are transmitted into the bloodstream of humans via direct contact with contaminated urine of animal reservoirs or indirectly by contaminated water and soil (Benacer, et al., 2013).

Leptospirosis is a significant zoonotic disease caused by Leptospira, a gram-negative spirochete, affecting a wide range of mammals, including both wild and domestic species. The clinical symptoms of leptospirosis typically present as a general febrile illness and lack distinctive features for accurate diagnosis. Consequently, leptospirosis is frequently misdiagnosed at first as meningitis or hepatitis (Johnson, 1996). After an average incubation period of 5 to 14 days (range 2 to 30 days), the disease presents with a wide range of non-

specific symptoms: fever, headache, chills, muscle aches, nausea or/and vomiting, diarrhea, abdominal pain, cough, jaundice, conjunctival suffusion, and sometimes rash (CDC, 2024). If left untreated, patients may develop kidney failure, jaundice, respiratory distress or failure, liver failure, and meningitis. In some cases, death may occur.

Identification and classification of leptospirosis are essential for effective surveillance and control. WHO defines cases as suspected, probable and confirmed based on several criteria:

Table 1 - Leptospirosis Case Definitions (WHO, 2024)

Suspected	Probable	Confirmed
• Suggestive epidemiological context (e.g. cyclone and/or flooding, exposure events such as adventure sports) • Clinical manifestations associated with leptospirosis include a **sudden onset of fever, chills, red eye irritation (conjunctival suffusion), headaches, muscle pain (myalgia), jaundice, potential heart or kidney failure, and lung bleeding.**	An individual who meets the criteria for a suspected case **and** the presence of *Leptospira* immunoglobulins type M (IgM) in a serum sample detected by serology (e.g. IgM enzyme-linked immunosorbent assay (ELISA)).	An individual who meets the criteria of suspected case **confirmed by laboratory tests**: • Seroconversion or a four-fold or higher rise in titre detected by serological techniques (e.g. microscope agglutination technique (MAT) or IgM ELISA) in consecutive serum samples; **or** • Detection of *Leptospira* DNA from a clinical specimen by polymerase chain reaction (PCR); **or** Demonstration of *Leptospira spp.* in tissue.

Leptospirosis progresses through two main phases: the leptospiremic (or septicemic) phase and the leptospiruric (or immune) phase, each characterised by the presence of *Leptospira* bacteria in different parts of the body and corresponding immune responses, which can make diagnosis and treatment difficult (Singh, 2007).

a. Leptospiremic phase (septicemic phase)

   In the leptospiremic phase, the *Leptospira* bacteria disseminate throughout the body, becoming present in the bloodstream and cerebrospinal fluid. This acute phase is characterized by sudden onset symptoms, including fever, intense headaches, muscle pain, and nausea, typically lasting around 4 to 7 days. During this period, a systemic infection is apparent, and diagnosis can be made by detecting Leptospira in blood or cerebrospinal fluid samples. The body responds by activating its immune system and producing specific antibodies (IgM and IgG), which are valuable for early diagnosis through serological testing.

b. Leptospiruric phase (immune phase)

The leptospiruric phase begins after an asymptomatic period and is marked by a recurrence of fever and possible central nervous system involvement, including meningitis. During this phase, *Leptospira* bacteria migrate from the bloodstream to the kidneys, where they colonize renal tubules and are excreted in urine, with shedding durations varying by host. Severe cases, often linked to the icterohemorrhagic serotype, may lead to Weil's disease, a severe form of leptospirosis (Johnson, 1996).

Antibodies typically develop within 2 to 12 days after the onset of leptospirosis. IgM antibodies appear early in the course of the disease, often being detectable within a week and sometimes as early as the third or fourth day. These antibodies usually peak during the third or fourth week and gradually decline over several months, often becoming undetectable within six months. In rare cases, low levels of IgM may persist for several years (Figure x) (Suwannin, et al, 2024).

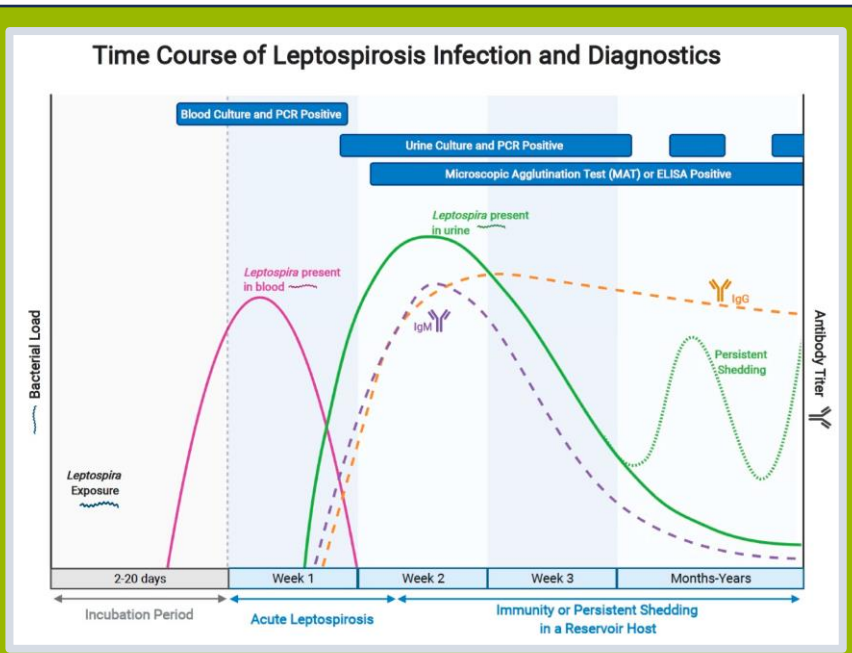


Figure 1. Duration of Leptospira infection and investigations at different stages of leptospirosis (Source: https://www.sciencedirect.com/science/article/abs/pii/S0147957123001509)

As infection spreads to organs such as the lungs, liver, kidneys, heart, skin, muscles, and cerebrospinal fluid, it may lead to complications like vasculitis, interstitial nephritis, jaundice from liver dysfunction, pulmonary hemorrhage, interstitial myocarditis, and muscle damage (Gvajaia et al, 2023; Koçak et al, 2018; Singh, 2007) . During the leptospiremic and leptospiruric phases, the kidneys are a primary target, as the bacteria invade mucocutaneous barriers, triggering antibody production and urinary shedding (Hinjoy, et al, 2019). While leptospires are cleared from systemic organs during the immune phase, they

persist in the kidneys, contributing to acute kidney injury (AKI) characterized by tubulointerstitial nephritis, often associated with microbial components, hyperbilirubinemia, or rhabdomyolysis. Chronic bacterial presence in renal tubules can lead to chronic tubulointerstitial nephritis (CTIN) and fibrosis, potentially progressing to chronic kidney disease (CKD). Recognizing asymptomatic leptospirosis-related kidney disease is therefore essential for diagnosing CKD of unknown origin, particularly in endemic regions.

Pathogen

Leptospirosis is a communicable disease affecting both animals and humans, caused by infection with *Leptospira*, a genus in the order Spirochaetes and the family *Leptospiraceae*. The typical dimensions of these bacteria are 0.1 µm in diameter and 6 to 20 µm in length. The *Leptospira* genus is characterized by flexible, spiral-shaped cells with distinctive hooked ends and two internal flagella that allow motility to facilitate migration across tissue barriers. The bacterial cell wall contains lipopolysaccharide (LPS), similar to other Gram-negative bacteria. While the heritability of leptospirosis remains unclear, structural variations in LPS contribute to the identification of over 200 serovars within *Leptospira* (Haake, et al., 2021; Verma, et al., 2020).

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Reservoir and Transmission

Rodents are an important reservoir for Leptospira, however, most mammals, including dogs, horses, cattle, pigs, and many wildlife species, can be infected and shed the bacteria in their urine (CDC, 2024). Leptospires are transmitted through abrasions or cuts in the skin, conjunctiva and mucous membranes, or macerated skin from prolonged water exposure (Mohammed, et al, 2011; CDC, 2024). Humans can be infected by direct contact with urine or reproductive fluids from infected animals, through contact with urine-contaminated freshwater sources or wet soil, or by consuming contaminated food or water. Infection rarely occurs through animal bites or human-to-human contact.

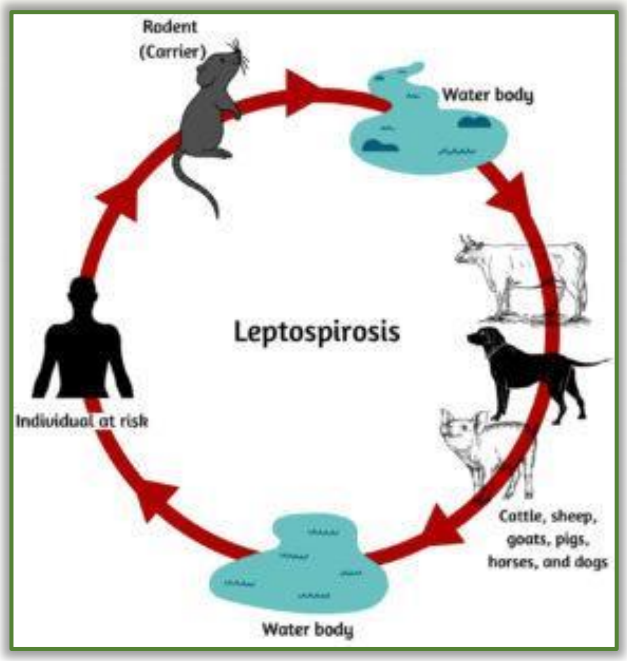


Figure 2. Transmission cycle of leptospirosis
(Source: https://microbiologyjournal.org/molecular-diagnostic-methods-for-the-detection-of-leptospirosis/)

Leptospires enter the host through skin lesions or small cuts, as well as through mucosal surfaces. Once inside, they enter the bloodstream and spread to various organs, eventually colonizing the kidneys. While many agricultural, domestic, and wild animals can harbor leptospirosis, the primary reservoir hosts responsible for transmitting the disease to humans are rodents (such as rats and mice), pigs, cattle, and dogs. These reservoir animals shed leptospires from their kidneys into the environment, where the bacteria can survive for weeks or months in freshwater or mud in moist or shady places. Humans can become infected through direct contact with these infected animals or indirectly through contact with contaminated water or soil.

Clinical Presentation

After exposure to the bacteria that cause leptospirosis, it takes 2-30 days for a person to become ill. Leptospirosis in humans may show a wide variety of symptoms and signs including: fever, severe headache, myalgias, conjunctival suffusion, jaundice, general malaise, stiff neck, chills, abdominal pain, joint pain, anorexia, nausea, vomiting, diarrhoea, oliguria/anuria, haemorrhages, skin rash, photophobia, cough, cardiac arrhythmia, hypotension, mental confusion, psychosis, and delirium (WHO, 2003). Many of these symptoms may be mistaken for other illnesses. In severe cases, leptospirosis can lead to organ failure, such as kidney or liver failure, while some people have no symptoms (CDC, 2024a). While many cases of leptospirosis are mild, a small proportion of cases develop severe leptospirosis, including icteric leptospirosis, haemorrhagic pneumonitis, and aseptic meningitis (Singh, 2007).

a. Icteric leptospirosis (Weil's disease)

In some patients, the septicemic phase progresses to severe icteric leptospirosis with renal failure. Jaundice, a key severity marker, typically appears on days 4–6 and peaks within a week, caused by hepatocellular necrosis, cholestasis, and tissue hemorrhage. Elevated bilirubin with mildly raised transaminases is characteristic. Renal failure, often oliguric, is the most serious complication and main cause of death, though non-oliguric cases have a better prognosis. Manifestations range from pyuria, albuminuria, and hematuria to severe renal failure.

Symptoms include worsening anorexia, vomiting, hiccups, mental disturbances, severe bleeding, and cardiac or pulmonary issues. By the second week, patients may be jaundiced, uremic, hemorrhagic, and comatose, with mortality in severe cases reaching 15–40%. Recovery in milder cases begins in the second week, but jaundice resolves more slowly.

b. Haemorrhagic pneumonitis

Pulmonary haemorrhage, a serious complication of icteric leptospirosis, usually occurs in the second week but can occur as early as 24-48 hours after the onset of illness. Symptoms begin suddenly with high fever (100-105°F), headache, body aches and a dry cough that becomes bloody within 2-3 days. This is followed by breathlessness and a toxic appearance with tachycardia, tachypnea and occasionally hypertension.

Fine crepitations, initially at the bases of the lungs, rapidly progress to involve both lung fields. Massive haemoptysis may lead to asphyxia and death, with a mortality rate of 50-70% in late presentations. Chest radiographs show bilateral alveolar opacities, typically denser in the middle and lower zones, with findings ranging from isolated opacities to extensive consolidation. Radiological abnormalities resolve within a week without permanent damage.

c. Aseptic meningitis

Leptospiral meningitis presents with a number of symptoms, including fever, headache, photophobia, vomiting, and meningeal irritation (e.g., neck stiffness, Kernig's sign, and Brudzinski's sign). A cerebrospinal fluid (CSF) analysis typically reveals lymphocytic pleocytosis (10–1000 cells/μL), elevated protein (10–200 mg/dL), and normal glucose levels. Convulsions, focal neurological signs, and encephalitis are uncommon and have an excellent prognosis for meningitis cases. Death is extremely rare and is usually linked to encephalitis. Distinctive leptospiral features, such as myalgia, conjunctival suffusion, and bleeding tendencies, are often present on careful examination.

4 Epidemiology

Clinical Diagnostic

The diagnosis of leptospira infection involves three primary approaches: general laboratory findings, indirect methods, and direct methods (WHO, 2003; Verma, et al, 2020).

1. **General clinical laboratory findings**

   Initial nonspecific assessments include blood, urine, and cerebrospinal fluid (CSF) analysis. Indicators such as leukocytosis, thrombocytopenia, elevated creatinine, urea, liver enzymes, bilirubin, and alkaline phosphatase in blood, along with proteinuria, pyuria, microscopic hematuria, and CSF abnormalities (pleocytosis, xanthochromia) may suggest leptospira infection (Budihal, 2014). However, specific microbiological or serological tests are needed for confirmation, though access to such tests may be limited . Bacterial isolation from tissues like the liver, kidneys, and eyes can confirm severity but is challenging, and needs more tests for diagnosis.

2. **Direct diagnostic methods**

   a. Microscopy

   Direct microscopy techniques, including dark field phase contrast microscopy, are used to identify leptospira in body fluids such as blood, urine, and CSF (Figure 3). The leptospira can be recognized by their distinctive morphology-thin, bright rods that are actively moving-and their characteristic rapid spinning and jerking movements (Verma, et al, 2020). A significant limitation of this method is that a minimum concentration of approximately 10 cells/ml is required for visualization; furthermore, the likelihood of obtaining a positive result diminishes to 90% if the infection has progressed beyond one week. Analyzing false positives and negatives with this diagnostic approach can also be quite challenging (Picardeau, 2014).

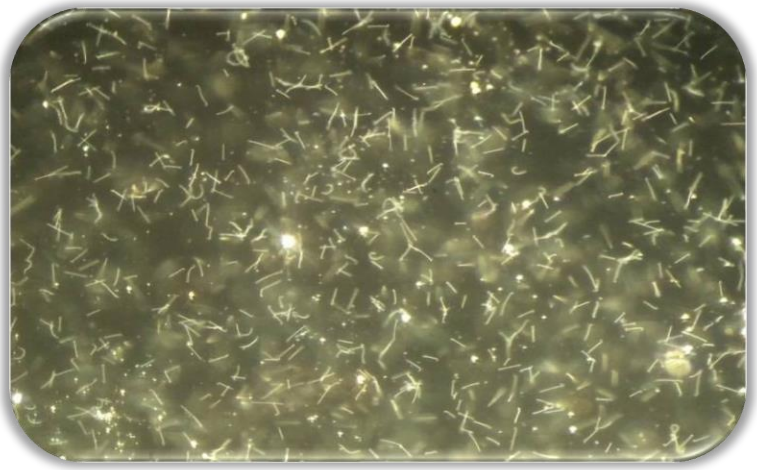


Figure 3. Leptospira cells observed under a microscope

b. Culture

Leptospire isolation relies on the sample type and disease stage (WHO, 2003). Blood culture for leptospires should be performed within the first 10 days of illness and before antibiotics are administered. Aseptically collected venous blood is ideally inoculated at the bedside into culture bottles containing *Leptospira* medium. Small inocula, using a few drops of blood, are distributed among several tubes containing 5 ml of medium each, as large volumes may inhibit bacterial growth. Cultures are incubated at 30°C and monitored for 4-6 months.

Leptospires may be observed by dark-field microscopy and isolated by culture by inoculating 0.5 ml cerebrospinal fluid into 5 ml semi-solid culture medium during the first weeks of illness.

During the leptospiruric phase, which begins about a week after illness onset and coincides with rising antibody levels, urine is the preferred sample for isolating leptospires. Wild and domestic animals in the carrier state may intermittently shed leptospires in urine or kidney tissue for years or even a lifetime. Fresh midstream urine should be collected and inoculated into culture medium within two hours of voiding, as urine acidity reduces leptospire viability. One drop of undiluted urine is added to a tube containing 5 ml of medium, or the urine may be centrifuged, and the pellet resuspended in medium before preparing serial dilutions. Cultures are incubated similarly to blood cultures.

c. Molecular methods

Molecular techniques, such as direct Polymerase Chain Reaction (PCR) and its variants (e.g., nested PCR and PCR/RFLP targeting 16S rRNA), enable rapid diagnosis using patient fluids or cultures during both early and recovery stages (Figure 4). These methods can detect leptospiral DNA at concentrations as low as 10 organisms. For example, PCR identified 39.08% of cases in a study of 103 patients with unexplained meningitis, outperforming ELISA (3.88%) and MAT (8.74%). Combining PCR with ELISA further enhances diagnostic sensitivity (Merien, et al, 1995; Ooteman, 2005, Croda, et al, 2007).

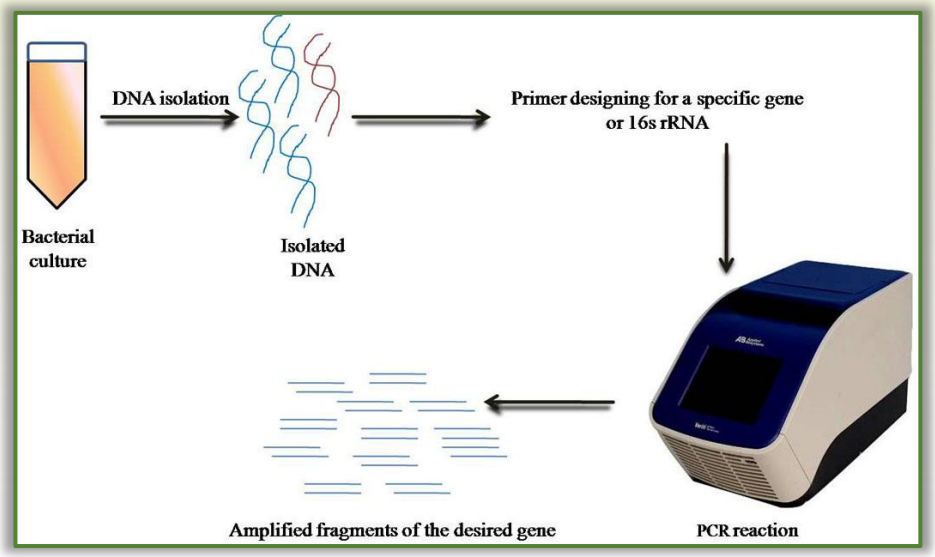


Figure 4. Schematic representation of PCR

Despite these advantages, PCR-based diagnostics face limitations such as the inability to identify the specific infecting serovar (48, 49). Additionally, when attempting to diagnose the organism directly from blood samples using PCR, host DNA can interfere due to non-specific primer binding. The presence of ions and proteins in blood can also inhibit the activity of DNA polymerase, particularly with Fe^{3+} ions (50).

3. Indirect methods

Serological methods are widely employed for diagnosing leptospirosis, typically becoming effective after the sixth day following the onset of symptoms. The most common techniques used for detecting serum antibodies include the Microscopic Agglutination Test (MAT), Enzyme-Linked Immunosorbent Assay (ELISA), and the Lepto Dipstick Assay.

a. Microscopic agglutination test (MAT)

The Microscopic Agglutination Test (MAT) evaluates antibodies in the blood of suspected leptospirosis patients by observing their interaction with live leptospiral antigens. In this procedure, a 7 to 12-day-old culture of leptospira is mixed with patient serum in well plates, and agglutination is then assessed under a dark field microscope (Figure 5).

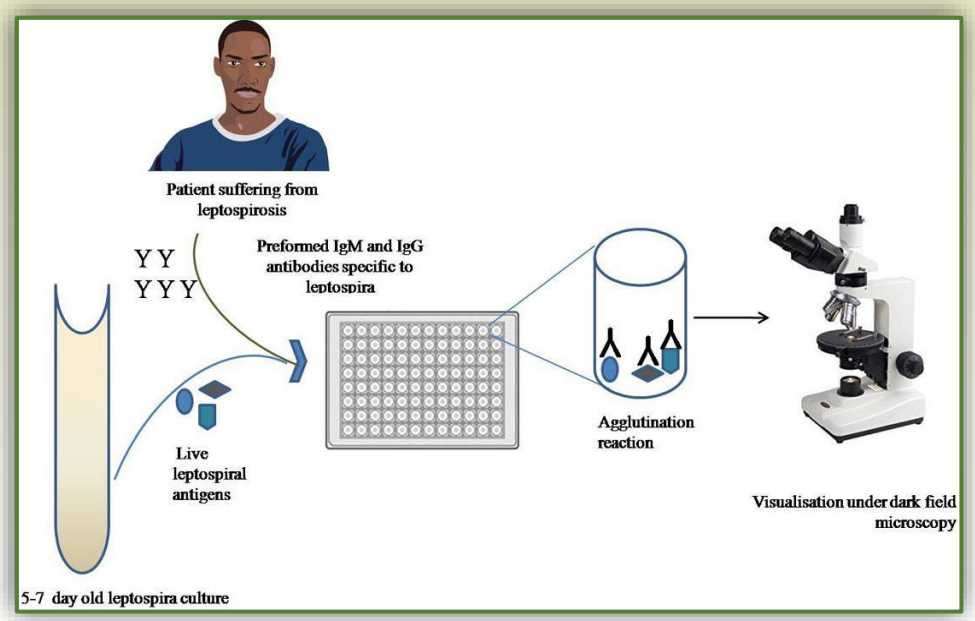


Figure 5. Schematic representation of microscopic agglutination assay (MAT) (Source: https://www.imrpress.com/journal/FBL/25/9/10.2741/4872/htm)

The Microscopic Agglutination Test (MAT) is regarded as the gold standard for diagnosing leptospirosis due to its high sensitivity. However, it requires a broad range of serovars to account for the antigenic diversity of Leptospira species. Consequently, MAT is not effective in the early stages of the disease, as specific antibodies may not yet be present or may exist at very low titers, leading to false-negative results. Furthermore, if a patient has previously been infected with a different serogroup, the diagnosis can become even more complicated due to the anamnestic response, where the first rise in antibody titer is directed against the serovar from prior exposure.

Although MAT is routinely used as a diagnostic test for leptospirosis in clinical laboratories, because of the numerous major difficulties linked with this high standard, new approaches must be considered.

b. Enzyme-linked immunosorbent assay (ELISA)

ELISA also detects IgM antibodies appearing in the blood however; MAT is used as the reference test (Figure 4). One of the primary advantages of ELISA over MAT is that it does not require live antigens for diagnosis. However, ELISA has limitations; testing a single serum sample from suspected patients is insufficient for confirming the disease. A follow-up test after two weeks is necessary to validate the results.

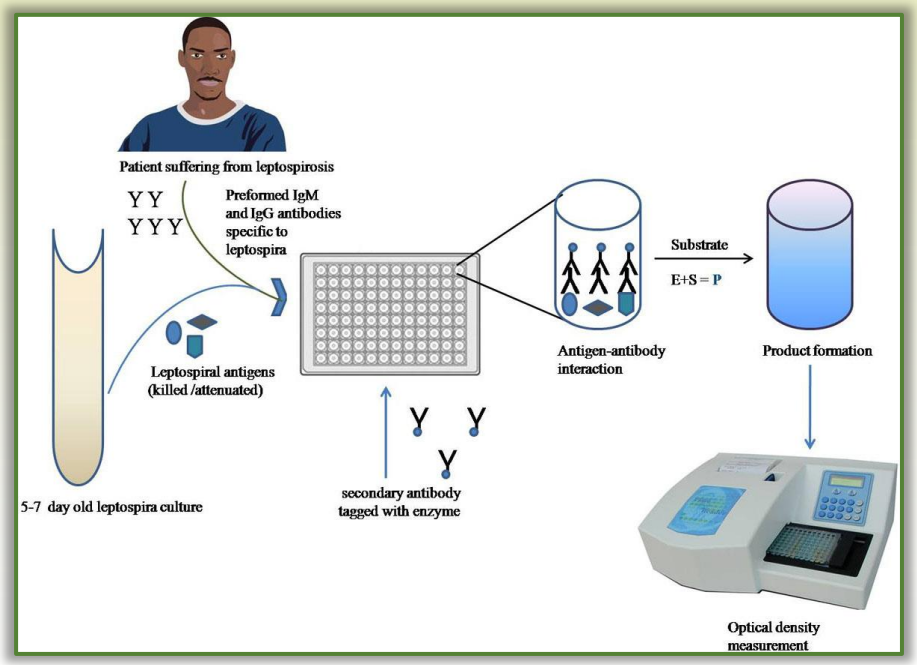


Figure 6. Schematic representation of ELISA
(Source: https://www.imrpress.com/journal/FBL/25/9/10.2741/4872/htm)

The formation and detection of IgM antibodies take time, which can hinder early diagnosis. Additionally, IgM antibodies have a prolonged persistence in serum, increasing the likelihood of both false positives and false negatives (56). To address these issues, an in-house variant of ELISA has been developed that utilizes formalin-treated or boiled Leptospira fainei as the antigen to specifically detect leptospira-specific IgM antibodies in patient sera.

c. Indirect haemagglutination assay (IHA)

The Indirect Hemagglutination Assay (IHA) is a method used to detect antigen-antibody interactions specific to the genus Leptospira in serum samples from suspected patients. This test operates on the principle of passive agglutination, where erythrocytes are coated with antigens that interact with soluble antibodies present in the patient's serum. The formation of a granular ring of agglutinated complexes is then observed in vitro, typically using microtiter plates (Figure 5) (Lizer, et al, 2017).

IHA offers several advantages over traditional methods like MAT. It is a rapid and straightforward procedure that does not require live antigens, making it easier to perform. However, it has lower specificity and sensitivity compared to MAT. A significant limitation of IHA is the requirement for sufficient antibody levels in the patient's serum, which can take approximately eight days to develop. This delay restricts its utility in diagnosing leptospirosis during the early stages of infection (Goris, et al, 2013).

Risk Factors and Risk Groups

Exposure to leptospirosis varies depending on contact with infected animals or contaminated environments, often influenced by occupational, recreational, or social activities (WHO, 2003). Examples include:

a. **Agricultural workers:** Cattle farmers during milking or handling infectious materials; pig farmers while tending pigs; rice and vegetable farmers through contact with contaminated water or soil.
b. **Animal handlers:** Veterinarians, pet keepers, abattoir workers, and butchers during interactions with infected animals, carcasses, or secretions.
c. **Water-related occupations:** Sewer workers exposed to contaminated sewage, sugar cane workers in fields with rodent activity, and miners in rat-infested mines.
d. **Recreational and daily activities:** Children playing in contaminated yards, villagers using untreated water, and individuals swimming or engaging in outdoor sports in contaminated environments.
e. **Specialized roles:** Laboratory staff and field researchers working with leptospirosis or other zoonotic pathogens.

Global Situation

Leptospirosis is a global disease, most prevalent in tropical and subtropical regions with heavy rainfall. It primarily occurs in areas where humans are exposed to the urine of infected animals or environments contaminated by infected urine (WHO, 2003). The disease has a wide geographical distribution due to the wide range of mammalian hosts that harbour and excrete the spirochete agent from their renal tubules (Costa, et al, 2015). The seriousness of leptospirosis is demonstrated by the fact that every year, approximately 10,000 severe cases require hospitalisation worldwide, with a high mortality rate. In addition, another study estimated that approximately 853,000 symptomatic cases occur annually worldwide (Taylor, 2015). Globally, the incidence ranges from 0.1 to 10 cases per 100,000 annually, but during outbreaks or in high-risk groups, it can exceed 50 per 100,000 (WHO, 2003).

Leptospirosis exhibits a wide range of clinical manifestations, from mild flu-like symptoms to severe and potentially fatal illness. It can mimic other diseases such as dengue fever, typhoid, viral hepatitis, and other viral hemorrhagic conditions. While jaundice (icterus) is a common symptom, it is also associated with other liver diseases, such as hepatitis, making it difficult to recognize as a sign of leptospirosis. In some severe cases, jaundice may be absent, but complications like severe pulmonary hemorrhage can develop early in the disease. Such cases have been increasingly reported in recent years. Diagnosis requires laboratory tests, which are not always accessible. As a result, leptospirosis remains underdiagnosed and underreported (WHO, 2003).

The incidence of leptospirosis is lower in developed regions than in developing areas, where outbreaks often follow heavy rainfall or flooding, increasing exposure to contaminated water (Verma, et al, 2020). Floods in countries such as Bangladesh, India and Sri Lanka have caused rodent-infested sewers to overflow, increasing the risk of infection. A notable outbreak occurred in Central America following Hurricane Mitch in 1998. The disease is also associated with occupational and recreational activities, with outbreaks reported among athletes in Illinois (12%), Malaysia (44%), and during triathlons in Germany (2006) and Austria (2010).

Leptospirosis has been endemic in India since the early 20th century, with frequent outbreaks in coastal regions of Gujarat, Maharashtra, West Bengal, Orissa, Kerala, Tamil Nadu, Karnataka, and the Andaman Islands. Cases peak during the monsoon season during October to November (Holla, et al, 2018; Jenna, et al, 2004). Notable outbreaks include 1,516 cases in Karnataka in 2007 and 130 deaths in southern Gujarat within two months in 2011. Recently, 209 cases with 12 deaths were reported in Kochi, Kerala, and 16 deaths in Surat and Valsad, Gujarat. These events highlight the disease's severity and the need for improved diagnostic tools (Verma, et al, 2020).

The World Health Organization's (WHO) Leptospirosis Epidemiology Reference Group (LERG) was set up to understand the global impact of leptospirosis, including how much disease and death it causes and its overall burden on health. As there is not enough data, the LERG reviewed studies, mostly from hospitals, that focus on more severe cases that require hospitalisation (Torgerson, et al, 2015). This means that many mild cases, which are much more common, were not counted. Based on the data, it is estimated that there are about 1.03 million cases of leptospirosis worldwide each year, resulting in about 58,900 deaths. These figures were used to calculate the overall impact of the disease in terms of years of life lost or lived with the disease, known as Disability-Adjusted Life Years (DALYs).

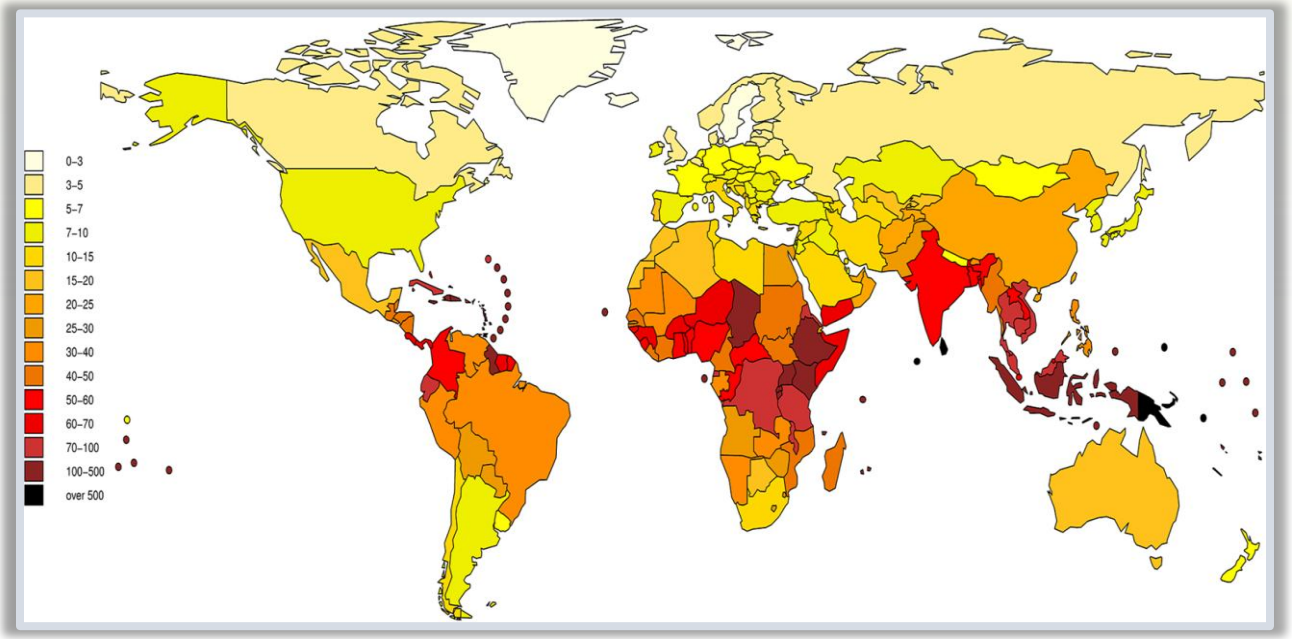


Figure 7. Burden of leptospirosis in terms of DALYs/100,000 per year.
(Source: Torgerson, et al, 2015 (https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0004122)

Burden of Leptospirosis in the ASEAN Region

Leptospirosis is periodically reported across several countries in the ASEAN Region, with its prevalence varying by country based on public health awareness and decision-making. Most cases occur during the rainy season in Indonesia and Thailand. Significant outbreaks have been documented in Jakarta (2003), while seasonal outbreaks frequently follow heavy rainfall and flooding in northern Thailand (WHO, 2003).

Brunei Darussalam

From 2007 to 2017, Brunei Darussalam reported a total of five cases of leptospirosis, with three cases in 2013, and one case each in 2014 and 2015. No deaths from leptospirosis were reported during this period. (Brunei Darussalam MoH, 2019).

Cambodia

Leptospirosis is an endemic cause of illness in Cambodia with most cases occurring during the rainy season, May through October, when flooding is common (CDC, 2024). The estimated annual incidence of leptospirosis in the country varies across studies. A previous study in Kampong Cham province indicates a 27% seroprevalence of leptospirosis among febrile patients (Hem et al, 2016). Another study in South-Central Cambodia on undifferentiated fevers in ambulatory patients in a rural healthcare setting found 20.8% seroprevalence of IgM leptospirosis (Kasper, et al, 2012)

Indonesia

In 2022, Indonesian Ministry of Health issued a circular urging heightened vigilance against rodent-borne diseases, including leptospirosis (Indonesian MoH, 2022). This initiative focuses on surveillance and control of rodent populations as vectors of the disease. Priority is given to the areas with a high potential of outbreaks, such as flood-prone regions, rice fields, and other high-risk locations. The effort aims to prevent and control the spread of these diseases more effectively.

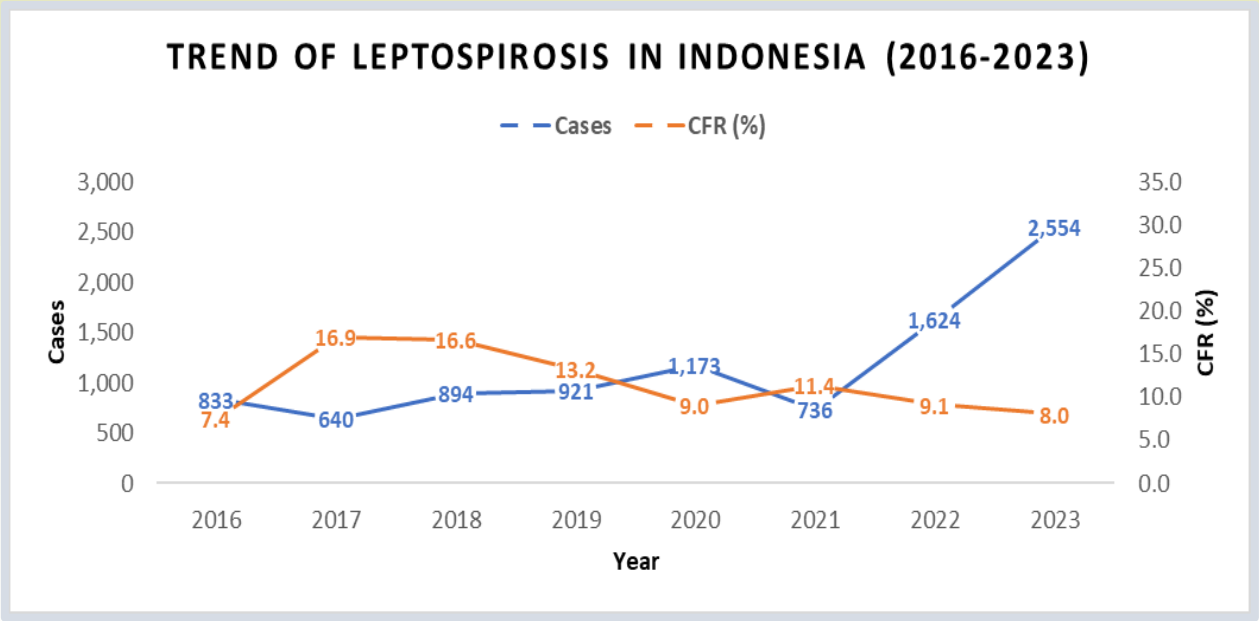


Figure 8. Trend of Leptospirosis in Indonesia (2016-2023)
(Source: MoH Indonesia)

In 2023, the Indonesian government recorded a total of 2,554 cases of leptospirosis in 12 provinces. The provinces in which cases were reported include DKI Jakarta, West Java, Central Java, Yogyakarta Special Region, East Java, Banten, North Kalimantan, South Sulawesi, East Kalimantan, Riau Islands, Bali, and Maluku (MoH Indonesia, 2024). From the reported cases in 2023, 205 resulted in death, with a case fatality rate (CFR) of 8%. This represents a significant increase from the preceding two years, 2021 with 736 cases and 2022 with 1,624 cases (Figure 8). The downward trend in fatality rates suggests an improvement in case management.

Lao People's Democratic Republic

Leptospirosis remains a significant public health concern in Lao People's Democratic Republic (Lao PDR). A study conducted in 2017 reported a seroprevalence of 23.9% among rural populations aged 15 and older, indicating a notable level of exposure to the disease in these communities (Ladien, et al, 2017).

Malaysia

In order to obtain the actual disease burden, leptospirosis is made a notifiable disease in Malaysia, the country has implemented hospital-based surveillance, as well as serosurveillance and active surveillance measures. For the purpose of surveillance, the State

Health Departments must compile a database for Leptospirosis. This database must have information on possible sources of infection (Malaysia MoH, 2011).

As a response for outbreaks, all cases are investigated and control measures are taken wherever possible. During an outbreak, the District Health Office should also investigate the clinical cases. All symptomatic cases in an outbreak should be admitted to hospital for laboratory confirmation and treatment. All outbreaks must be notified to National Crisis Preparedness and Response Centre (CPRC), then all outbreak preliminary reports to the CPRC, Disease Control Division by e-mail, text/sms, and fax using the report form within 24 hours.

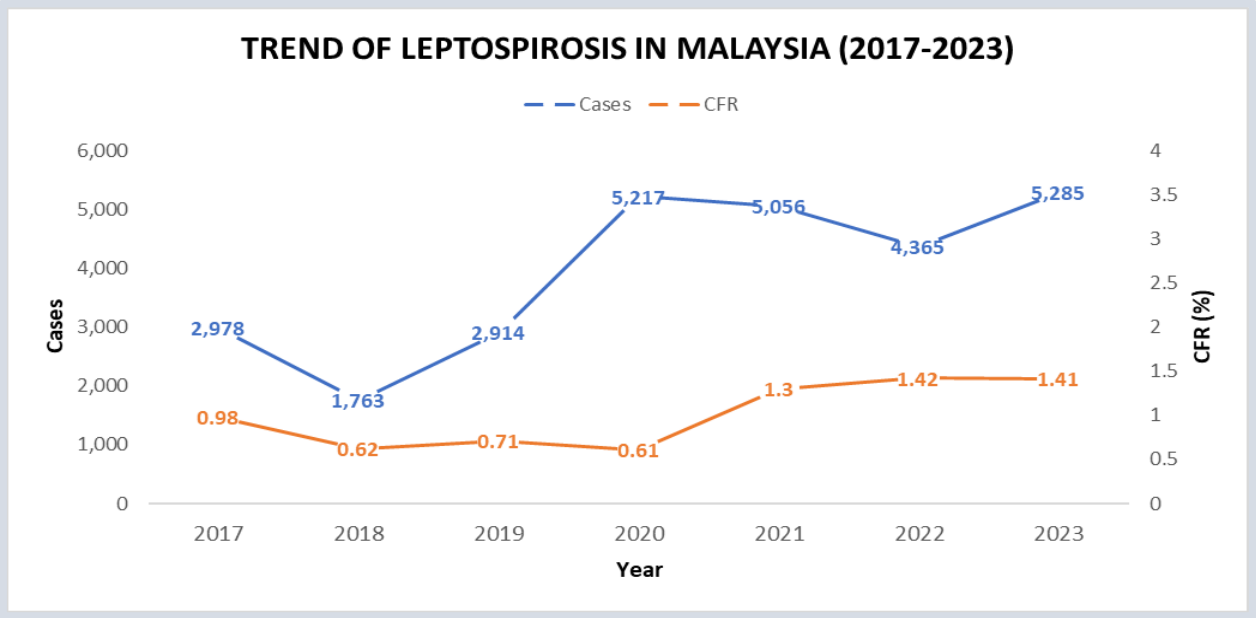


Figure 9. Trend of Leptospirosis in Malaysia (2017-2023)
(Source: MoH Malaysia)

Malaysia experienced a notable decline in leptospirosis cases from 2017 to 2018, followed by an increase and peak in 2013 (WHO, 2023). Mortality cases also increased from 2020 to 2023 and fluctuated, trending upward until 2022 (Figure 9) (MoH Malaysia, 2024).

Myanmar

Leptospirosis is a significant public health concern in Myanmar, particularly in areas with poor sanitation and frequent exposure to contaminated water sources. In Myanmar, leptospirosis remains under-diagnosed. Laboratory diagnostic capacity should be strengthened especially in district and township-level hospitals. The animal sector should also be strengthened for surveillance of leptospirosis.

A recent serosurvey among abattoir workers revealed that 6.7% tested seropositive for Leptospira antibodies (95% CI: 3.5%, 11.4%) (SEAOHUN, 2022). The study highlighted a widespread lack of awareness about leptospirosis, its modes of transmission, and prevention. Health education programs focused on these aspects should be implemented promptly and intensively. Furthermore, the use of personal protective equipment (PPE) among workers was found to be substantially low. Occupational factors such as not wearing PPE and heavy exposure to animal blood were significantly associated with seropositivity. The study emphasizes the need for abattoir workers to consistently wear appropriate PPE to reduce their risk of infection.

Philippines

The Philippines has developed a National Action Plan for the prevention and control of leptospirosis, primarily through the LepCon program (CPHUPM, 2024). This initiative aims to address the rising incidence of leptospirosis in the country, particularly during the rainy season when outbreaks are more common.

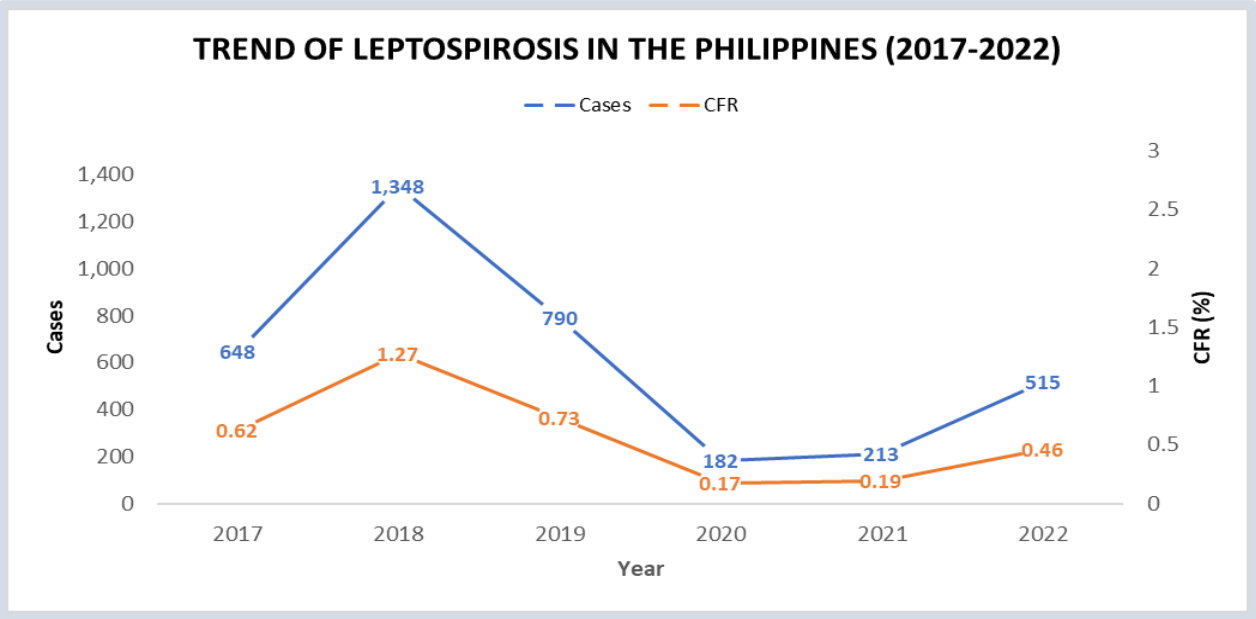


Figure 10. Trend of Leptospirosis in the Philippines (2017-2022)
(Source: Philippines DoH)

The Philippines recorded peak cases in 2018 with 1,348 reported cases and then consistently reported fewer cases to 182 cases in 2020 (Figure 10). However, cases re-emerge with a total of 515 cases reported in 2022. Compared to 2018, the case fatality rate decreases to 0.46% in 2022, demonstrating the country's successful leptospirosis treatment efforts over the years (Philippines DoH, 2023)

Singapore

In Singapore, the control measures for leptospirosis are managed by the National Environment Agency (NEA), which implements a comprehensive approach to minimize the disease's risk. The key components of their strategy include:

1. **Integrated Vector Management**: Evidence-based strategies are used to control vector populations and keep the incidence leptospirosis low.
2. **Surveillance Programs**: Continuous surveillance helps detect emerging vector-borne diseases, enabling timely interventions. NEA inspects residential and commercial properties to remove breeding sites, reducing disease transmission.
3. **Public Education Campaigns**: Educational initiatives aim to raise awareness of leptospirosis and its transmission, informing the public about preventive measures to reduce infection risk.
4. **Research and Development**: NEA invests in laboratory and field research to improve understanding of leptospirosis and develop effective risk intervention tools. This includes studying the prevalence of *Leptospira* spp. in local rodent populations, which are key reservoirs for the bacteria.
5. **Collaboration with Health Authorities**: NEA collaborates with health authorities to ensure effective monitoring and management of leptospirosis cases, enabling a coordinated response to outbreaks.

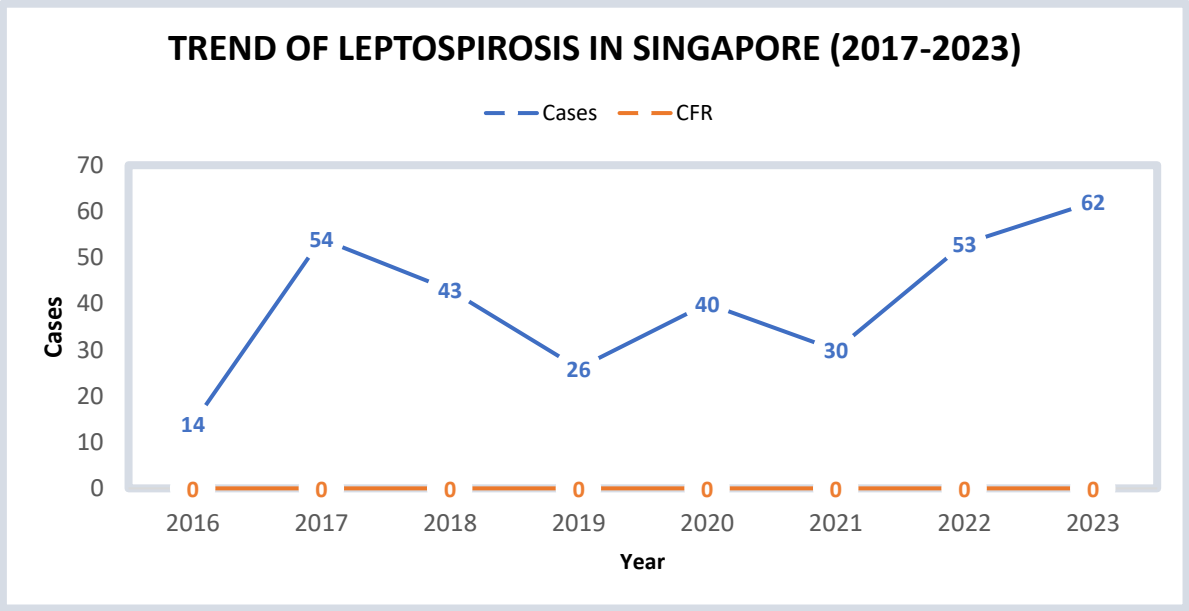


Figure 1. Trend of Leptospirosis in Singapore (2016-2023)
(Source: MoH Singapore)

After a surge in 2017 with 54 cases, the country showed a decline in cases until 2019. However, cases fluctuated, with 62 reported in 2023 (Figure 11).

Thailand

In 2011, the Department of Disease Control, under the Ministry of Public Health, introduced the District Strengthening Disease Control standard to enhance disease prevention and control efforts (Viroj, et al, 2021). The Ministry of Public Health established the 4E2C procedure for the prevention and control of leptospirosis [15]. Currently, efforts to manage leptospirosis are guided by the 2015 National Communicable Diseases Law, emphasizing collaboration among government agencies at the provincial level to plan and implement disease prevention and control strategies.

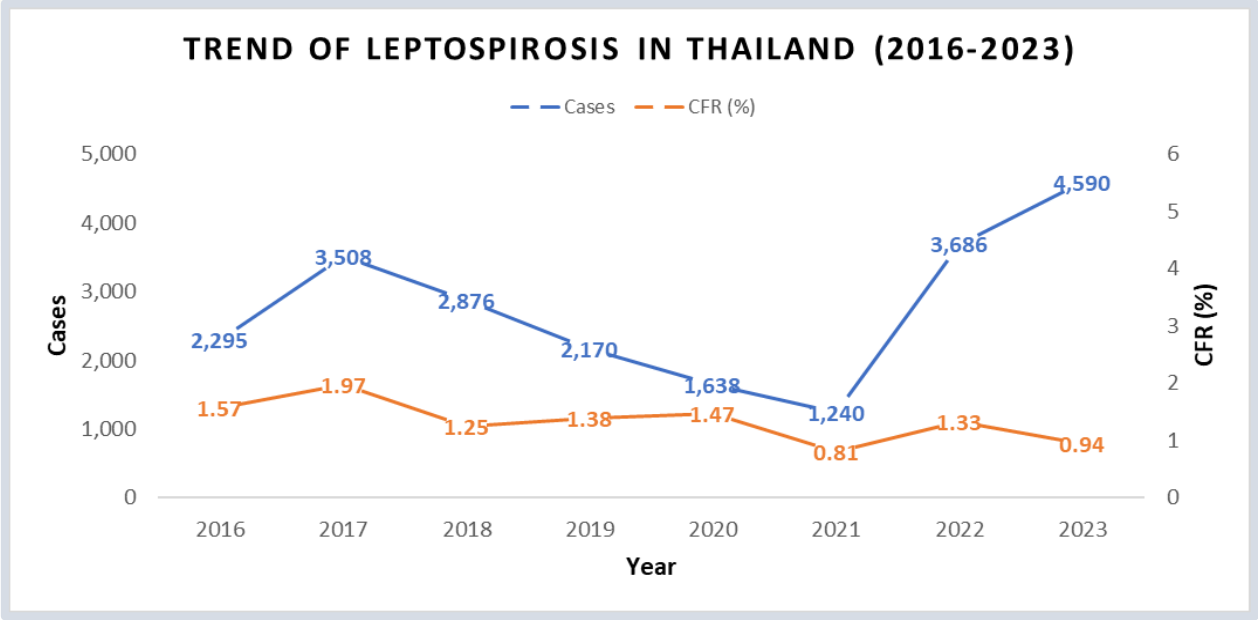


Figure 12. Trend of Leptospirosis in Thailand (2016-2023)
(Source: MoH Thailand)

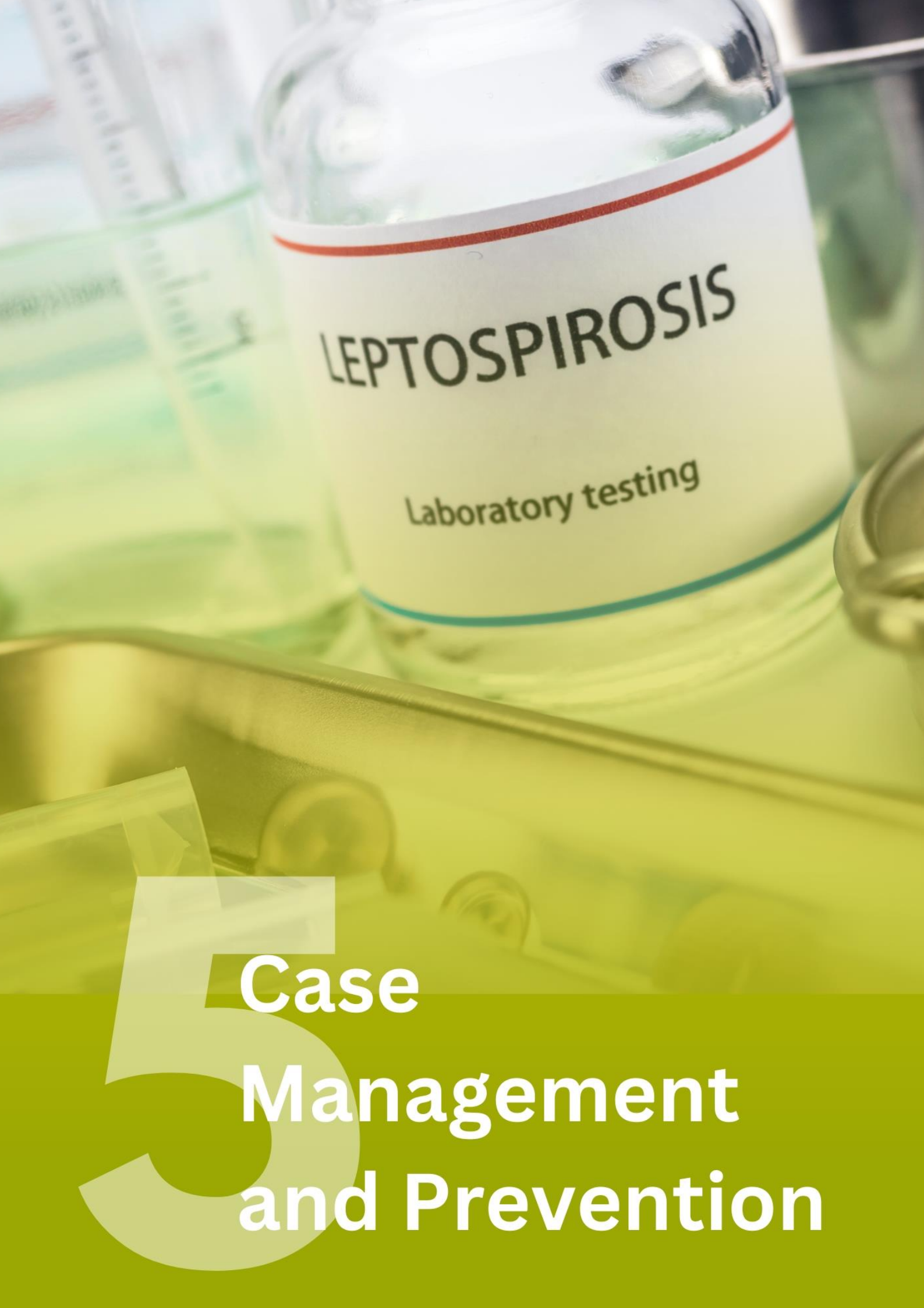
Following a downward trend since 2018, a total of 1,240 cases were reported nationally in 2021 (Figure 12. However, there is a significant increase in the last two years, with 3,686 cases in 2022 and 4,590 cases in 2023 (Figure 12). Annual fatality rates remain low at 0.8% to 2% (Thailand MoH, 2024).

Viet Nam

Leptospirosis has been studied in Viet Nam and the surrounding region, but further research is needed to fully understand the disease and assess its prevalence. It remains under-recognized due to the challenges in both clinical and laboratory diagnosis. While much of the disease seems to be waterborne and linked to heavy rainfall and flooding, the

understanding of the associated risks is still incomplete (Vietnam Ministry of Agriculture and Development, 2016).

Surveillance data showed that leptospirosis was confirmed or considered likely in 1.8% (68 cases) and 6.5% (248 cases) of patients using the microscopic agglutination test (MAT) or enzyme immunoassay (ELISA-IgM), respectively (Tokarevich, et al, 2022). Over 30% of patient serum samples tested positive for IgM antibodies to Leptospira (ELISA data). The highest number of laboratory-confirmed cases was in Thai Binh (2.3%), followed by Ha Tinh (2.0%) and Can Tho (1.0%). The proportion of cases considered "probable for leptospirosis" was even higher: 8.5% in Ha Tinh, 7.1% in Can Tho, and 7.0% in Thai Binh.



5 Case Management and Prevention

Case Management

As soon as leptospirosis is detected, therapy with effective antibiotics should begin, ideally before the fifth day following the commencement of sickness (WHO, 2003). The WHO highlights the need for high doses of intravenous antibiotics in severe cases. It is, however, debatable if antibiotics are beneficial after the fifth day of the illness. Regardless of when the sickness first appeared, the majority of doctors treat patients with antibiotics.

Leptospirosis requires prompt clinical intervention, as diagnostic delays can exacerbate the disease's progression (WHO, 2009). Serological tests often do not become positive until about a week after symptom onset, and cultures may take several weeks to yield results. Therefore, treatment should begin without waiting for laboratory confirmation. Hospitalization is necessary for severe cases, where aggressive supportive care is critical. Maintaining fluid and electrolyte balance is a primary focus. For cases involving renal failure, haemodialysis or peritoneal therapy is recommended. When pulmonary hemorrhagic manifestations occur, mechanical ventilation is essential to manage respiratory distress effectively. Advancements in supportive care and the availability of dialysis in recent years have contributed to a reduction in leptospirosis-related mortality. Early clinical management remains key to improving patient outcomes in severe cases (WHO, 2009). Antibiotics used for treating leptospirosis cases are:

a. Severe cases of leptospirosis should be treated with high doses of intravenous penicillin.
b. Less severe cases can be treated with oral antibiotics such as amoxicillin, ampicillin, doxycycline or erythromycin.
c. Third-generation cephalosporins, such as ceftriaxone and cefotaxime, and quinolone antibiotics also appear to be effective.

Prevention

To reduce the risk of leptospirosis infection, the World Health Organization (WHO, 2009) recommends several measures:

a. Avoiding contact with animal urine, diseased animals, or a contaminated environment.
b. Worn protective clothes should, if exposure is likely, such as through work or pleasure
c. Wounds should be covered with waterproof bandages
d. Raise the general public's, risk groups', and healthcare professionals' knowledge of the illness to enable prompt diagnosis and treatment.

Doxycycline has been reported to provide some protection against leptospirosis. Although human vaccines are available in some countries, they only protect against the specific serovars contained in the vaccine. These vaccines usually contain inactivated leptospires and are serovar-specific. In areas where multiple serovars are common, vaccines may combine the most common serovars. However, protection is limited to the serovars included in the vaccine and they do not provide long-term immunity or cross-protection against different serovars. Commercial human vaccines have been developed in countries like France and Cuba, but these vaccines do not offer lasting protection or broad immunity against all strains of the disease.

Dogs, pigs and cattle can be vaccinated with vaccines made from killed leptospires. These vaccines provide serovar-specific protection, meaning they protect against specific strains of the bacteria. Although vaccination can prevent disease, it does not always prevent animals from becoming carriers, particularly in the kidneys where the bacteria can persist without causing symptoms.

Control Measures

Because of the large number of serovars and infection sources and the wide differences in transmission conditions, the control of leptospirosis is complicated and will depend on the local conditions (WHO, 2009). Control can be achieved by controlling the reservoir or reducing infection in animal reservoir populations such as dogs or livestock. Control of wild animals may be difficult. Preventive measures must be based on knowledge of the groups at particular risk of infection and the local epidemiological factors. Prevention and control should be targeted at the infection source, the route of transmission between the infection source and the human host, and/or infection or disease in the human host.

It is important to establish what animal species are the infection sources in a particular area. Control measures can then be targeted to the local reservoir species of animals. Such measures include:

a. The reduction of certain animal reservoir populations, e.g. rats;
b. The separation of animal reservoirs from human habitations by means of fences and screens;
c. The immunization of dogs and livestock;
d. The removal of rubbish and keeping areas around human habitations clean;
e. Encouraging people not to leave food around, especially in recreational areas where rats may be present.

6 Control Measures Strategy

Strategy to Eliminate Zoonoses

While economic development has enhanced global well-being, it has frequently led to ecosystem degradation, environmental harm, and adverse effects on animal welfare (FAO, UNEP, WHO, and WOAH, 2022). Land use changes, unsustainable agriculture, deforestation, and biodiversity loss are undermining ecosystems and heightening health risks at the human-animal-plant-environment interface, especially for vulnerable communities. High-risk exposures occur in contaminated environments, such as rivers or floodwaters, and during activities like farming, forestry, or waste clearing without adequate protection. These issues are compounded by urbanization, complex food systems, poor waste management, trade, and the climate crisis. Urgent action is needed to reshape human-environment interactions, prioritize health and sustainability, and advance the Sustainable Development Goals.

Addressing health issues at the human-animal-environment interface requires collaboration across sectors and disciplines, as no single sector can tackle zoonotic diseases and shared health threats alone (FAO, WHO, and WOAH, 2019). The One Health approach fosters collaborative, multidisciplinary, and multisectoral efforts to address urgent, ongoing, or potential health threats at subnational, national, regional, and global levels. It emphasizes balance and equity among all relevant sectors and disciplines to ensure effective and sustainable solutions.

a. Strategic planning and emergency preparedness

Strategic planning and emergency preparedness was developed to involve all sectors relevant to the response to zoonotic diseases in a collaborative, multisectoral, One Health approach both to strategic planning for priority endemic zoonotic diseases and routine zoonotic disease events and to preparedness for zoonotic disease emergencies (FAO, WHO, and WOAH, 2019). ***Strategic planning*** is the process by which a strategic goal is combined with the steps necessary to reach that goal. It is an essential base for building the capabilities and capacities, including allocating resources, required to address both priority zoonotic diseases and zoonotic disease events and emergencies. ***Emergency preparedness*** builds upon national capabilities and capacities and ensures a country is ready to manage zoonotic disease events or emergencies that require more than a routine response. Strategic planning and emergency preparedness will not be effective unless they are complete before an event or emergency. Preparedness efforts must be put in place before a zoonotic event to both reduce ongoing risks and maintain a state of readiness.

b. Surveillance for zoonotic diseases and information sharing

The primary objective of a coordinated zoonotic disease surveillance system is to detect zoonotic disease events by integrating data from all relevant sectors. This approach facilitates the timely sharing of information across sectors to enable coordinated responses, prevention strategies and mitigation efforts.

Results from a surveillance system coordinated across all relevant sectors is critical for understanding disease burden, monitoring trends, as an early warning system, and to support outbreak investigation and response. Key considerations for the design and implementation of such a system for zoonotic disease surveillance and information sharing include:

a. **Inclusion of all relevant domains:** Since zoonotic diseases can spread between humans, animals (including vectors), and their shared environment, surveillance must encompass these domains to ensure comprehensive coverage.
b. **Understanding context and risk factors:** The context in which zoonotic diseases emerge influences their severity, spread, and impact. Identifying risk factors for transmission among humans, animals, and vectors enables informed, evidence-based decision-making.
c. **Sectoral alignment and collaboration:** Establishing and maintaining coordinated mechanisms may face challenges, such as differing perceptions of benefits across sectors due to variations in pathogenicity, misunderstandings about the environment's role in transmission, or conflicting mandates among government sectors and ministries.
d. **Addressing disparities in resources and capacity:** Imbalances in capability, capacity, and resources among sectors often result in a disproportionate burden on those with greater capabilities. Efforts should focus on equitable resource allocation to ensure sustainable collaboration.

c. Coordinated investigation and response

Coordinated investigation and response aims to bring together expertise and capacities in all relevant sectors to investigate emerging or endemic zoonotic diseases in humans, animals, and the environment and to evaluate the extent of disease and guide decision making and appropriate responses across all relevant sectors to provide timely and effective action to control and prevent further spread of disease. This approach includes the following steps:

1. Clarifying each sector’s roles and responsibilities
2. Determining required coordinated investigation
3. Developing a decision tool to determine initiation and scale of response

4. Developing protocols for implementing coordinated investigation and response
5. Organizing field investigation
6. Organizing response

The Tripartite organizations-comprising the Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO), and the World Organisation for Animal Health (WOAH)-have collaborated for decades to address risks at the human-animal-environment interface (FAO, UNEP, WHO, and WOAH, 2022). In February 2021, the United Nations Environment Programme (UNEP) joined the Tripartite, reinforcing the critical role of the environmental dimension in the One Health approach.

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