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Incidence and distribution of human leptospirosis in the Western Cape Province, South Africa (2010-2019): a retrospective study

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Incidence and distribution of human leptospirosis in the Western Cape Province, South Africa (2010-2019): a retrospective study

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Abstract

Introduction: *leptospirosis is an emerging zoonosis of global importance. In South Africa, the infection is an underreported public health concern, with limited information on its incidence and distribution. This study investigated the incidence of human leptospirosis in Western Cape Province (WCP) between 2010 and 2019, and compared the incidence based on seasonal and demographic factors.* ***Methods:*** *a retrospective study was conducted with data on leptospirosis diagnoses in WCP obtained from the National Health Laboratory Services. With the provincial population sizes as the denominator, incidence of leptospirosis was estimated and expressed as cases per 100,000 population. Negative binomial regression was used to estimate the effect of sex, season, and year on the incidence of leptospirosis.* ***Results:*** *two hundred and fifty-four (254) cases of leptospirosis were reported between 2010 and 2019, with the highest number of cases being in 2015 and the annual incidence ranged between 0.15 and 0.66/100,000 population. Males had a higher incidence compared to females (0.55 vs. 0.25/ 100,000 population; incidence rate ratio (IRR) 2.2, 95% CI: 1.66,3.03). The 18-44 age cohort had the highest average incidence (0.56/100,000 population), while the ≤17 age cohort had the lowest incidence (0.07/100,000 population). The 18-44 (IRR 8.0, 95% CI: 4.65,15.15) and ≥45 (IRR 7.4, 95% CI: 4.17,14.17) age cohorts were more at risk of infection compared to ≤17 age cohort.* ***Conclusion:*** *leptospirosis is an important zoonosis in WCP disproportionately affecting males and the productive age demographic groups. These findings should enhance targeted prevention and provoke further investigation on the importance of environmental and socioeconomic factors on leptospirosis burden.*

Introduction

Leptospirosis is an emerging, global zoonosis with an estimated 1.03 million cases and 58,900 deaths occurring annually [1-4]. The disease is caused by pathogenic spirochetes Leptospira species currently reported comprising 66 different species with more than 300 serovars [5]. The infection in humans is associated with varying clinical manifestations ranging from a mild self-limiting febrile illness to severe illness characterized by dysfunction of multiple organs such as liver, kidneys, lungs, and the brain [6] potentially leading to pulmonary hemorrhagic syndrome and acute kidney injury due to Weil´s disease [3,7,8]. Consequently, the infection is mostly underdiagnosed and underreported [9] because its clinical manifestation is similar to commonly known febrile illnesses such as malaria. Despite the life-threatening nature of leptospirosis, there is little published data on morbidity associated with the infection [2,3,10] contributing to its neglected status. The risk of leptospirosis infection among humans occurs either through direct exposure to urine or aborted tissues of wild or domestic reservoir animals such as rodents and livestock/pets [2,11], or through indirect exposure such as contact with contaminated water, soil, and food [11,12]. In South Africa, a recent prison outbreak of leptospirosis was associated with exposure of inmates to rat urine in an overcrowded prison. Due to the predominant modes of transmission, leptospirosis is regarded as an occupational hazard affecting mainly farmers, sewer workers, veterinarians, and military personnel [9,13-16]. However, the transmission patterns are changing because there are increasing reports of leptospirosis in the general population. These cases are due to recreational exposures such as camping, kayaking, adventure travelling, hiking, cave exploration and other activities done in infected water [9,13,15,17].

Globally, tropical regions as well as resource limited settings are reported to have a higher burden of leptospirosis compared to temperate regions [3]. However, in Africa, few countries have data and reports on human leptospirosis [16,18] and research studies are scarce [3,4]. A previously published systematic review, of peer-reviewed studies conducted in Africa, reported a prevalence of acute human leptospirosis ranging from 2.3% to

19.8% among hospital patients presenting with febrile illness and an estimated total of 750,000 cases per annum [16]. It was further concluded in this study that the morbidity of human leptospirosis in Africa is likely to be high relative to other global regions [16]. The need of more studies on the occurrence of leptospirosis in Africa was emphasized in another systematic review by De Vries *et al.* [18] to reliably understand the extent of the problem. The incidence of human leptospirosis in South Africa has been suggested to be moderately high within the population [19-21]. Findings about the continued circulation of highly pathogenic *Leptospira spp.* among rodents suggests that the infection maybe an important underreported public health concern in the country [19,20]. A study conducted between 2009 and 2011 reported a seroprevalence that ranged from 9% to 12.5% among all clinical samples sent to the National Health Laboratories Services (NHLS) for IgM ELISA testing from all over the country [21]. Environmental conditions in Western Cape Province (WCP) South Africa, (the coastal, and temperate conditions with wet winters and warmer summers) have been suggested to favor transmission of pathogenic *leptospira* species L, *borgpetersenii* and L. *interrogans* traditionally associated with rats [2,19,20]. The most recent retrospective study conducted between 2005-2015, focused on patients presenting at a tertiary referral hospital in WCP, and a seroprevalence of 20% was reported [22]. Studies outside Africa have highlighted the influence of season, gender and age on the distribution and occurrence of human leptospirosis [23-25]. Such associations have scarcely been studied in Africa despite changes in climatic factors, demographic shifts, urbanization, and globalization [4,9,26-28]. The risk conferred by rodent infestation and overcrowding have been demonstrated in a recent leptospirosis outbreak that occurred in a prison in WCP, South Africa [20]. Despite this information, studies describing leptospirosis occurrence in relation to demographic and seasonal factors are lacking in WCP. To address these knowledge gaps, a retrospective study on human leptospirosis cases in the WCP, South Africa was conducted using data generated from diagnostic tests done in a public health care setting in Cape Town, South Africa. The study aimed at determining the incidence and trends of human leptospirosis over a 10-year period (2010-2019), with respect to year and seasonality and to describe the demographic characteristics of leptospirosis cases.

Methods

Study setting: Western Cape Province is located on the south-western coast of South Africa and is bordered by the Northern Cape and Eastern Cape Provinces. Western Cape Province has a population of approximately seven million inhabitants, with a female to male ratio of 1: 1.027, and three quarters of the population use public-sector healthcare services [29]. The province is approximately 129,462 km^2 and has a population density of 45 inhabitants per Km^2 [30]. Administratively, the province is divided into one metropolitan municipality (City of Cape Town) and five district municipalities (Central Karoo, Garden Route, Overberg, West Coast and Cape Winelands). The province has a diverse climate but is dominated by a Mediterranean climate with a cool, wet winter and a warm, dry summer and inland daily maximum temperature ranging between 20°C in winter to 32°C in summer and the mean annual rainfall <380 mm.

Study design and study population: a retrospective study was conducted by using data provided by the NHLS, on all human leptospirosis tests conducted at public healthcare facilities in the WCP, South Africa. The NHLS does ELISA IgM serological testing on all serum samples of patients who are clinically suspected to be having a leptospirosis infection. Specimens from suspected patients are collected from different public healthcare facilities within the province and sent to a central NHLS laboratory in Cape Town. In this analysis, data included are from patients who had laboratory confirmed leptospirosis between 1st January 2010 and 31st December 2019.

Data collection: human leptospirosis cases were considered for all ELISA IgM serological tests that were positive for Leptospirosis during the study period (2010 to 2019). ELISA IgM testing is the serological test conducted on all samples submitted to NHLS for leptospirosis screening and is sensitive in detecting new onset of illness [9]. Patient data extracted included the patient´s age, sex, year, date of test (year, month, and day) and the name of the health facility that submitted the specimen for testing. The population sizes based on year, sex, and age in WCP for the 10-year period were extracted from the Western Cape Department of Health population circular H102 of 2020 [31]. This data was used as the denominator when calculating the incidence of leptospirosis infection.

Statistical analysis: all human leptospirosis cases were tabulated according to sex, age, season, and year of occurrence (2010-2019) and their frequency and proportions were calculated. The date when the test was done was used to assign the case to a particular year and season. Season was categorized as summer (1st December-28/29th February), autumn/fall (1st March-31st May), winter (1st June-31st August), and spring (1st September-30th November). The variable year was conceptualized as a consecutive 12-month period from 1st January to 31st December, thus there were ten categories for year (2010 to 2019). The incidence proportion of human leptospirosis for each year (2010-2019) was estimated and expressed as leptospirosis cases per 100,000 population. The incidence proportion by sex and age group as well as for each season of the year was also estimated. The Kruskal-Wallis Rank Sum Test was used to compare the average annual incidence between seasons of the year, age groups and between years. The Wilcoxon Rank Sum Exact Test was used to compare the average annual incidence between sex demographics. The negative binomial regression was used to estimate the effect of sex, gender, year of occurrence and season of the year on the incidence of human leptospirosis over the study period. This is a suitable regression model to use instead of the traditional Poisson regression in situations where modelling involves a count variable that is over-dispersed (the mean is less than the variance). The results were presented as incidence rate ratios (IRR) with 95% confidence intervals (CI). The cut-off value for statistical significance was 0.05. All statistical analysis was conducted using R software version 1.2.5033.

Ethical considerations: ethical approval was obtained from the University of Cape Town Human Research Ethics Committee (UCT-HREC) (reference number: HREC REF: 303/2021). The WCP approval was granted by Groote Schuur Hospital Research Ethics Committee. The approval to use data from NHLS database was given by the NHLS Academic Affairs and Research office (reference number: PR2118953).

Results

Distribution of leptospirosis cases in Western Cape Province, 2010-2019: during the 10-year study period (2010-2019), a total of 254 cases of human leptospirosis were recorded by the NHLS for persons in WCP, South Africa. The annual number of cases differed significantly across the years (p-value <0.001) with the highest number of cases recorded in 2015 (42 cases, 16.5%) and 2012 having the lowest (9 cases, 3.5%) (Table 1). Months in the fall season had the highest number of cases recorded (March: 30 cases; May: 28 cases) over the 10-year period while months in Spring has the lowest cases recorded (August and September: 16 cases) (Figure 1A). Around sixty-eight percent of the cases were males with the overall male to female ratio 2.136: 1 and the number of cases differed significantly by sex (p-value <0.001) (Table 1). The median age of the observed cases was 37.0 years inter quantile range (IQR) 28.0-48.0). 64.2 % of the cases were in the 18-44-year-old age group, 30.7% in ≥ 45-year-old age group while 5.1% in the ≤17-year-old age group over the 10-year study period and this differed significantly (p-value <0.001) (Table 1).

Incidence of leptospirosis in the Western Cape Province, 2010-2019: the incidence of leptospirosis fluctuated widely across the 10 years. The annual incidence ranged from 0.15 to 0.66 cases per 100,000 population, with an average annual incidence of 0.40 cases per 100,000 population. The incidence followed a downward trend between 2010 and 2012, however, there was an increase in the incidence from 2013 which peaked in 2015 (0.66 cases per 100,000 population). This was followed by a gradual decrease between 2015 and 2019 except for 2018 where the annual incidence was higher than the one observed in 2017 (Figure 1B). Overall, the incidence was significantly high among males compared to females (average incidence among males: 0.55 cases per 100,000 population; average incidence among females: 0.25 cases per 100,000 population, p-values=0.004) (Figure 1C). During the entire study period, the incidence differed significantly across age groups (p-value <0.001) with the highest occurring in the 18-44-year-old (0.56 cases per 100,000 population) followed by ≥ 45 years-old age group (0.49 cases per 100,000 population) and ≤17-year-old age group (0.07 cases per 100,000 population) (Figure 1D). On average, the annual incidence was highest during fall season (0.12 cases per 100,000 population) and lowest in winter (0.08 cases per 100,000 population) over the 10-year period (Table 2). However, incidence of leptospirosis between the seasons of the year was not statistically significant.

Effect of sex, age, year, and season on leptospirosis incidence in WCP, 2010-2019: Table 3 shows the results from the multivariable negative binomial regression (MNBR) model that was run to identify factors associated with the incidence of leptospirosis during the 10-year period. The incidence rate of leptospirosis among the male demographic was 2.2 (95% CI: 1.66,3.03) times higher than among females during the entire study period. The model results indicated that on average the incidence rate of leptospirosis among 18-44 and ≥ 45 age groups was 8.0 (95% CI: 4.65,15.15) and 7.4 (95% CI: 4.17,14.17) times higher than the incidence rate among ≤17 years age group. The incidence was significantly lower in 2012 (IRR 0.25; 95% CI 0.11, 0.54), 2013 (IRR 0.34; 95% CI 0.16, 0.68), 2017 (IRR 0.53; 0.28, 0.98) and 2019 (IRR 0.47; 95% CI 0.24, 0.87) compared to the incidence in 2010. The incidence rate during the entire study period was not associated with season of the year.

Discussion

This study provides a first description of the incidence of human leptospirosis in the Western Cape Province (WCP), South Africa across a 10-year period. We report an average incidence of 0.40 leptospirosis cases per 100,000 population, ranging from 0.15 in 2012 to 0.66 in 2015 cases per 100,000. There was no overall increase in the annual incidence of leptospirosis, however, the incidence fluctuated widely across the 10-year period. The incidence was significantly higher in males compared to females. The 18-44-year-old and ≥ 45 years-old age groups had a higher incidence of the infection compared to the ≤17-year-old age group. The incidence was not related to season over the 10-year period. The annual incidence observed during this 10-year period lies within the range of the incidence that has been reported globally to be occurring in temperate regions (0.1-1 cases per 100,000 population) [31]. The cold wet winters and warm dry summers might allow transmission and survival of pathogenic Leptospira species [19]. Western Cape Province is known for its harsh drought, and different types of floods such as river floods, flash floods and these occur in each year at varying intensities [32]. Annual fluctuation in such environmental conditions could partly explain the observed wide fluctuation in the annual incidence of leptospirosis because increase in incidence is normally reported after occurrence of extreme weather events such as heavy rains and high temperatures [27,31,33]. In addition, rodent infestation, increased prevalence of infected rodents and overcrowded settings were reported as risk factors for human leptospirosis outbreak in a one of the prisons in WCP in 2015 [20]. This

outbreak could have contributed to the observed increase in the incidence in 2015. In a study conducted after this outbreak, Naidoo *et al*. further highlighted the importance of continued circulation of pathogenic *leptospira spp* among rodents in maintaining the status of leptospirosis transmission particularly in informal settlements [20].

Previous studies have indicated a significant relationship between leptospirosis incidence and seasonality [31,33,34]. In WCP, seasonality was not associated with the incidence of leptospirosis between 2010 and 2019, however the observed incidence in fall and summer was higher than that observed in winter and spring. This is consistent with some reports from other countries in temperate regions [31,35]. Studies on correlation between leptospirosis incidence and seasonality require consideration of other variables such as rodent seasonal population, temperature, rainfall, and other climate related parameters to be included in the analysis [34]. This could help in understanding the importance of the interaction of different environmental and climatic factors in determining the incidence of leptospirosis in resource limited settings. The overall incidence was significantly higher in males as compared to females during the study period. Similar results have been reported in both seroprevalence studies in Africa and in incidence studies conducted using surveillance data globally [23,35,36]. The higher incidence among males has been largely attributed to occupational or environmental exposure, whereby males engage in activities that may put them at higher risk of contracting the infection [33,37]. Epidemiological studies collecting data on occupation, underlying medical conditions, and place of settlement could aid in categorically establishing risk groups hence guiding policies on targeted prevention of leptospirosis. The incidence of leptospirosis was highest among those within the 18-44 and ≥ 45 -year-old age groups compared to those below ≤ 17 years of age. These findings are in line with a systematic review by Costa *et al*. that reported the highest incidence to be occurring among adult males aged 20-49 years [3]. The observed results also correspond with other studies, where incidence has been shown to be higher among the active adult population [35]. People belonging to the 18-44 age group would theoretically have an increased environmental exposure compared to those belonging to ≤17 age group, thus increasing their risk of being infected.

The data presented here are the first results to inform on the incidence trends and distribution of leptospirosis in WCP. The data covers a 10-year period, and highlights males and 18-44 age group as risk groups, hence could help to guide designing of preventive strategies and indicates need of a surveillance system for leptospirosis in WCP and South Africa. However, there are some study limitations that need to be considered. Firstly, the study utilized data collected from passive surveillance and from a public health laboratory setting excluding data from private laboratories, hence there is a great potential for underestimation of the real occurrence of leptospirosis in WCP. Some bias may still be inherent in the analysis due to ambiguity in clinical presentation; the latter contributes to underestimation of actual incidence. Secondly, the study describes leptospirosis in general and does not highlight the serovars circulating in South Africa. This was mainly because the data accessed used IgM ELISA for diagnostic purposes only. Thirdly, the analysis does not provide information on the geographical distribution of the cases within the province as such information was not included in provided data. Consideration of the geographical distribution of the incidence would have given insights into which specific districts are at risk, hence informing targeted interventions. Findings from this analysis highlight the continued circulation of leptospirosis infection within WCP with age and sex being significant risk factors for infection. However, there is need of a good knowledge about the epidemiology of leptospirosis (such as the geographical and seasonal patterns, the specific risk populations, circulating Leptospira strains and the importance of reservoir animals) [10] within the province to

improve prevention strategies, prediction, and detection of leptospirosis burden and outbreaks. For instance, future studies focusing on the impact of heavy rainfall, floods, seasonal fluctuation in weather-related factors, occupation, geographical location, and rodent dynamic parameters on leptospirosis incidence could help address the knowledge gaps on the actual burden of this emerging zoonosis.

Conclusion

In conclusion, the incidence of leptospirosis in WCP fluctuated between 2010-2019 with an outbreak in 2015. The incidence was strongly related to sex and age. These results show that leptospirosis is an important zoonosis within the province and potentially disproportionately affecting males and the productive age demographic groups. The findings, therefore, can guide targeted intervention strategies within the province to decrease the burden of human leptospirosis.

What is known about this topic

- *Leptospirosis is an emerging neglected zoonosis globally with an estimated 1.03 million cases and 58,900 deaths occurring annually;*
- *Few countries within Africa have data and reports on human leptospirosis and research studies are scarce;*
- *Studies describing leptospirosis occurrence and distribution in Western Cape are lacking, though the incidence in South Africa is reported to be moderately high.*

What this study adds

- *The paper reports the annual incidence of leptospirosis and how it has fluctuated from 2010 to 2019 in Western Cape, South Africa;*
- *The study has shown that males and 18-44 age group were more at risk of infection in Western Cape between 2010 and 2019;*
- *The study indicates need of more epidemiological studies focusing on impact of climatic, environmental, geographical, and rodent breeding on leptospirosis occurrence in South Africa.*

Competing interests

The authors declare no competing interests.

Authors' contributions

Jasantha Odayar assisted in conceptualisation of the study protocol, reviewed the data analysis and manuscript for final submission; Sipho Dlamini contributed to the conceptualisation of the study and review of the manuscript for final submission. Lynthia Paul contributed to conceptualisation of the study, assisted in data acquisition from National Health laboratory service, Western Cape, South Africa, reviewed the manuscript for final submission; Jacob Mugoya Gizamba: investigation, conceptualisation of the study, designed the study, analysed data, interpreted the results, prepared and the reviewed the manuscript for final submission. All the authors have read and agreed to the final manuscript.

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Tables and figure

Table 1: distribution of leptospirosis cases by age, sex, season, and year of occurrence in Western Cape Province South Africa (2010-2019)

Table 2: seasonal incidence of leptospirosis for the years 2010-2019, in Western Cape Province, South Africa

Table 3: multivariable negative binomial regression analysis results between year, season, sex, and age group with incidence of leptospirosis
Figure 1: distribution of leptospirosis in Western Cape Province (WCP), South Africa, 2010-2019

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Table 1: distribution of leptospirosis cases by age, sex, season, and year of occurrence in Western Cape Province South Africa (2010-2019)

Variables	**All cases (n=254) n (%)**	**p-value**
Age (years) median (IQR)	37.0 (28.0,48.0)	
Age group		
0-17	13 (5.1)	
18-44	163 (64.2)	
45>=	78 (30.7)	<0.001
Sex		
Male	173 (68.1)	
Female	81 (31.9)	<0.001
Season of the year		
Summer	64 (25.2)	
Fall	75 (29.5)	
Winter	53 (20.9)	
Spring	62 (24.4)	0.277
Year of occurrence		
2010	34 (13.4)	
2011	19 (7.5)	
2012	9 (3.5)	
2013	12 (4.7)	
2014	28 (11.0)	
2015	42 (16.5)	
2016	37 (14.6)	
2017	22 (8.7)	
2018	31 (12.2)	
2019	20 (7.9)	<0.001
IQR: inter quantile range; n: frequency		

Table 2: seasonal incidence of leptospirosis for the years 2010-2019, in Western Cape Province, South Africa				
Year	**Summer**	**Fall**	**Winter**	**Spring**
	***IP (95% CI)**	***IP (95% CI)**	***IP (95% CI)**	***IP (95% CI)**
2010	0.10 (0.02,0.19)	0.28 (0.14,0.41)	0.12 (0.03,0.21)	0.09(0.01,0.16)
2011	0.12 (0.03,0.21)	0.03 (-0.01,0.08)	0.07 (0.001,0.13)	0.10 (0.02,0.18)
2012	0.07 (0.001,0.13)	0.03 (-0.01,0.08)	0.02 (-0.02,0.05)	0.03 (-0.01,0.08)
2013	0.05 (-0.01,0.10)	0.05 (-0.01,0.10)	0.07 (0.001,0.13)	0.03 (-0.01,0.08)
2014	0.02 (-0.01,0.05)	0.10 (0.02,0.17)	0.14 (0.05,0.24)	0.19 (0.08,0.30)
2015	0.20 (0.09,0.31)	0.17 (0.07,0.27)	0.16 (0.06,0.25)	0.13 (0.04,0.21)
2016	0.18 (0.08,0.29)	0.21 (0.10,0.33)	0.03 (-0.01,0.07)	0.14 (0.05,0.23)
2017	0.12 (0.03,0.18)	0.09 (0.02,0.16)	0.08 (0.01,0.14)	0.06 (0.001,0.12)
2018	0.12 (0.04,0.20)	0.15 (0.06,0.24)	0.09 (0.02,0.16)	0.10 (0.03,0.18)
2019	0.04(-0.01,0.09)	0.07 (0.01,0.14)	0.07 (0.01,0.14)	0.10 (0.03,0.18)
Average incidence	0.10 (0.03,0.18)	0.12 (0.04,0.20)	0.08 (0.02,0.15)	0.10 (0.02,0.17)
IP: incidence proportion; CI: confidence interval: *IP estimated as cases/100000 population				

Table 3: multivariable negative binomial regression analysis results between year, season, sex, and age group with incidence of leptospirosis			
Variables	**IRR**	**95% CI**	**P value**
Year of occurrence			
2010	Ref	_	_
2011	0.543	(0.281,1.026)	0.061
2012	0.25	(0.106,0.536)	0.001
2013	0.337	(0.157,0.684)	0.003
2014	0.73	(0.402,1.314)	0.294
2015	1.033	(0.597,1.796)	0.907
2016	0.956	(0.546,1.677)	0.874
2017	0.53	(0.282,0.98)	0.046
2018	0.748	(0.418,1.334)	0.323
2019	0.466	0.244,0.872	0.019
Season of the year			
Winter	Ref	_	_
Spring	1.166	(0.765,1.782)	0.475
Summer	1.184	(0.778,1.808)	0.431
Fall/autumn	1.422	0.947,2.147	0.091
Sex			
Female	Ref	_	_
Male	2.239	(1.664,3.034)	<0.001
Age group			
≤17	Ref	_	_
18-44	8.045	(4.654,15.147)	<0.001
≥45	7.391	(4.167,14.169)	<0.001
IRR: incidence rate ratio; CI: confidence interval; ref: reference category; MNBR: multivariable negative binomial regression			

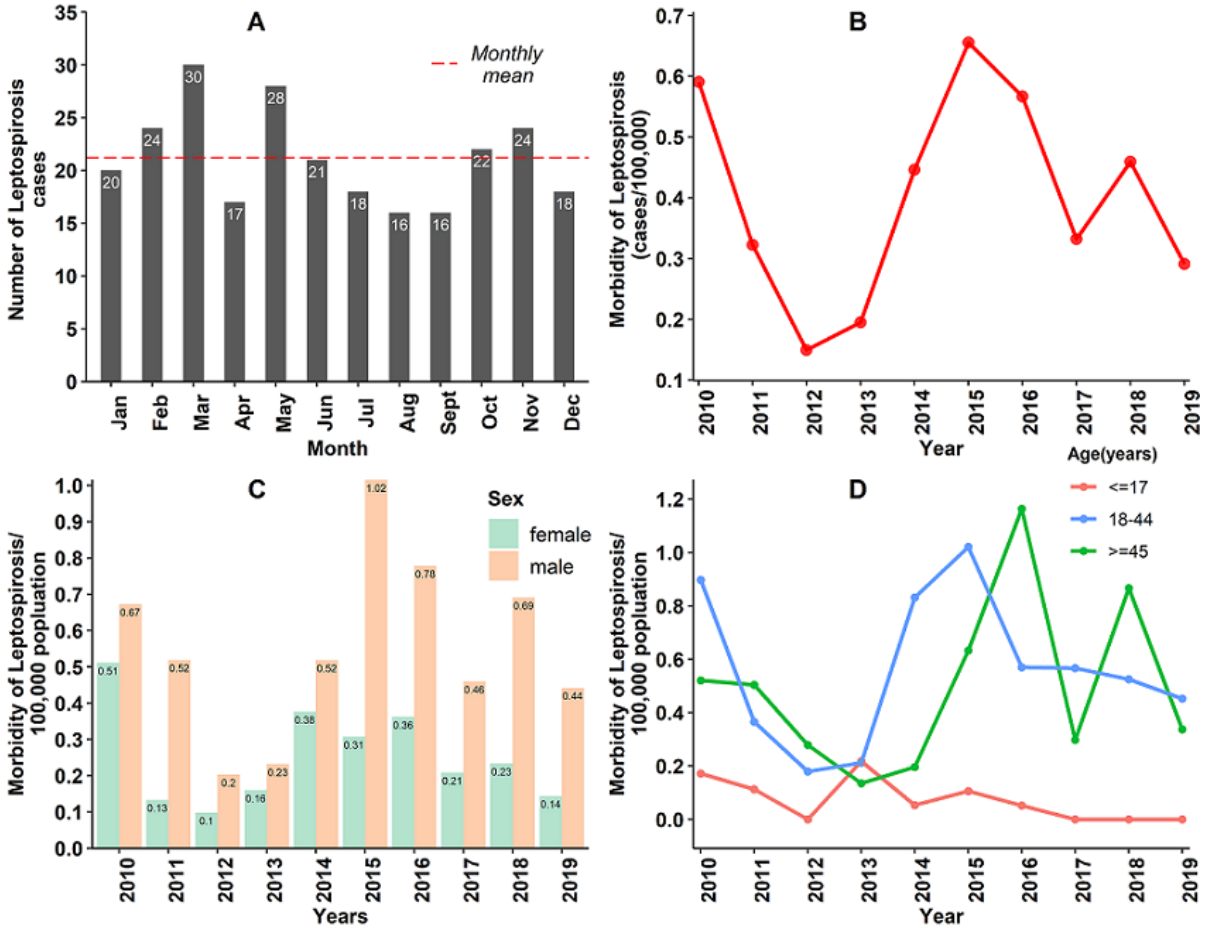

Figure 1: distribution of leptospirosis in Western Cape Province (WCP), South Africa, 2010-2019