Patterns of Scrub Typhus tests prescribed among the three Hospitals in Zhemgang District, 2019-2020: A record-based laboratory review study.

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Abstract

Introduction: Scrub typhus is a neglected life threatening acute febrile illness caused by bacteria Orientia tsutsugamushi and it is a vector-borne zoonotic disease. In 2009, scrub typhus outbreak at Gedu has awakened Bhutan on the awareness and testing of the disease.Information and data of the study highlights the need for in depth surveillance, awareness among prescribers and initiate preventive measures in the country. Methods: We used retrospective descriptive study through review of laboratory registers across three health centres in Zhemgang district, south central Bhutan. The laboratories registers have been transcribed into CSV file using Microsoft excel. Variables of interest were collected from the registers and then analysed using open statistical software R, (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.) And use of mStats package, (MyoMinnOo (2020). mStats: Epidemiological DataAnalysis. R package version 3.4.0.) Results: Of the total 922 tests prescribed for suspected scrub typhus in the three health centers in Zhemgang, only 8.2 % (n=76) were tested positive. Of these, Panbang Hospital had highest reported positive for scrub typhus with 56.6 %(n=43) followed by Yebilaptsa Hospital 35.5 %(n=27) and Zhemgang Hospital with 7.9 %(n=6). The female gender is comparably more affected as opposed to male with 57.9% (n=44) of the positive cases being female. The prevalence of scrub typhus seems to be affected by the seasonal variation as the months of Spring, Summer and Autumn together accounts for 98.7%(n=75) of total positive cases. The year 2019 noted significant scrub typhus cases accounting to 89.5 %(n=68) of the total positive cases over the two years. Conclusions:The overall tests tested positive of the scrub typhus infection within two years was 8.2%.

Introduction

Scrub typhus is a zoonotic and a rickettsial disease causing acute febrile illnesses. It is causedby a bacterium called Orientia tsutsugamushi. Scrub typhus rank among the foremost cause of suffering and death in developing countries[1].The disease is transmitted by infected chigger mites to humans. It is characterized by fever, nausea, vomiting, myalgia, lymphadenopathy, eschar, cough, headache, gastrointestinal symptoms and many other severe complications[1&2]. Diagnosis of scrub typhus is based on clinical manifestations and history of environmental exposure.Within first week of bite by infected mites, symptoms like chills, fever, rashes and lymphadenopathy will occur and serious complications of pneumonitis, pleural effusion, hepatomegaly, edema, acute kidney injury, acute respiratory distress syndrome and meningitis may follow in untreated patients[3].

Geographically, subtropical climate has highest incidence of Scrub typhus and was endemic disease to Taiwan in the year 2000-2004. It is commonly found in Asian countries like Pakistan, Afghanistan, Maldives,

Bangladesh, India and Japan[4]. Outdoor activities, agricultural works, and living near grassland and fields are associated high risk of exposure to Scrub typhus with overall fatality rate of 13.6%[5].Scrub typhus is the leading infectious diseases in Northern India during monsoon and post monsoon seasons[6].The transplacental spread of Scrub typhus was reported in India in a pregnant woman who has delivered preterm baby with other multi-organ failure like hepatosplenomegaly, meningitis and sepsis. Scrub typhus re-emergence in Maldives in 2002 has recorded 168 suspected with 10 confirmed deaths. Fatality rates range from 6% to 35% in untreated and missed diagnosis.

In Bhutan, the case was first detected at Geduin 2009. The case re-emerged in 2014 at one of the rural primary schools of Bhutan claiming two lives[7]. Scrub typhus is prevalence in Bhutan currently stands to 62 per 100000 population at risk[8].

Zhemgang experiences a mildly warm and temperate climate and lies in subtropical region. The people of the district depend on agriculture and livestock farming. The district had 17763 populations as far the 2017 national survey report. The district has twelve primary healthcare centres (PHCs), four sub posts and three hospitals. Only those three hospitals have laboratory services to diagnose Scrub typhus.

Investigating the patterns of scrub typhus tests in the three higher level health centres of the district and crucial in understanding the disease pattern, as well as physicians prescribing pattern. This will help to obtain deeper level of the disease picture in Zhemgang and is expected to help public health intervention in the district. There are few studies conducted on Scrub typhus in Bhutan but lacks data on region wise and district wise presentation.

This study aimed to: (1) assess patterns of tests prescribed for Scrub Typhus within the Zhemgang District across different health facilities, seasons, year and age of the study participants.

Methodology

Study site and design

We used retrospective descriptive study through review of laboratory registers across three health centres in Zhemgang district, south central Bhutan. The laboratory registers have been transcribed into CSV file using Microsoft excel. Variables of interest were collected from the registers and then analysed using open statistical software R, (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.) and use of mStats package, (MyoMinnOo (2020). mStats: Epidemiological DataAnalysis. R package version 3.4.0.)

Three health care centres included in the study lacks ELISA testing facility. However the tests were done with SD BiolineTsutsugamushiTest^{TM} rapid diagnostic test (RDT) kits in 2019 and Standard Q Tsutsugamushi IgM/IgG in 2020.The tests were done with SD BiolineTsutsugamushiTest^{TM} rapid diagnostic test (RDT) kits in 2019 and Standard Q Tsutsugamushi IgM/IgG rapid test kit in 2020which has underestimated sensitivity and specificity in accuracy of test results.

Sampling

All laboratory blood tests being advised for scrub typhus in three health centres in Zhemgang from January 2019 to December 2020 have been included in the study.

Analysis

The data was transcribed from the laboratory registers into Microsoft excel 2016 and exported as CSV file for analysis purpose. Data analysis was carried out using an open software R, (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.) and use of two packages, mStats package, (MyoMinnOo (2020). mStats: Epidemiological Data Analysis. R package version 3.4.0.) and dplyr (Hadley Wickham, Romain François, Lionel Henry and KirillMüller (2021). dplyr: A Grammar of Data Manipulation. Rpackage version 1.0.7. https://CRAN.R-project.org/package=dplyr)

Analysis included all explanatory variables which included the (1) age, (2) sex, (3) month of the tests advised and (4) the site of the health centers. While the review of registers for more than just the two years have been considered, it was not feasible as two of the health centers did not have the laboratory registers before 2019.

Information on main characteristics of tests advised was summarized based on the explanatory variable of age, sex, months/seasons, health centre and the test results. Primary outcome was test results defined as positive across different age groups, gender, health centres and season.We identified predictors of positive results using a multi-variable logistic regression model. Multiple models with all the predictor variables were tested and the final model was selected based on the lowest AIC score.

Results

In two years, from January 2019 to December 2020, a total of 922 tests to scrub typhus were advised in three health centres in Zhemgang District. The maximum age prescribed to the test was 94-year-old man in Panbang Hospital while the minimum age prescribed to the test was 1 month old also prescribed in Panbang Hospital. The test results for both of these cases were negative. The mean age for the tests prescribed in all the three health centres combined was 36.1±17.9 for both the genders.The mean age for women were slightly higher (37.03± 19.93) compared to men (35.06 ± 19.5).

Of 922 samples tested, 49 % (n=452) were male while 51% (n=470) were female. Of the total tests prescribed, 446 tests were prescribed in Yebilaptsa Hospital, 324 were prescribed in Panbang Hospital and 152 were tested in Zhemgang Hospital. 62.3% of the tests were carried out in 2019 which has drastically reduced the prescription by 2020 accounting to only 37.7%. The months of June, July, August and September saw the highest tests being prescribed while the months of December, January and February wereobserved with least number of tests prescribed. Of the total tests prescribed, only 8.2% (n=76) were confirmed to be positive. The descriptive summaries of the tests to the scrub typhus for the two years are described in table 1.

Table 1Scrub Typhus Tests in Zhemgang District, as described by individual variables in 2019 – 2020

Variable	Category	Total Tests	Percentage %	Cum. %
	Panbang Hospital	324	35.1	35.1
SITE	Yebilaptsa Hospital	446	48.4	83.5
	Zhemgang Hospital	152	16.5	100
YEAR	2019	574	62.3	62.3
	2020	348	37.7	100
SEX	FEMALE	470	51	51
	MALE	452	49	100
RESULTS	NEGATIVE	846	91.8	91.8
	POSITIVE	76	8.2	100

There were great variations in tests prescribed according to the seasonal changes. The summer and autumn months together accounted for 73.1% of the total tests prescribed as seen in table 2.

Table 2Total tests prescribed for scrub typhus according to the season in Zhemgang, 2019 - 2020

Seasons *	Total Tests Prescribed	Percentage of tests prescribed (%)	Cumulative Percent (%)
Autumn	**120**	**13**	**13**
Spring	**269**	**29.2**	**42.2**
Summer	**454**	**49.2**	**91.4**
Winter	**79**	**8.6**	**100**
Total	**922**	**100**	**100**

(Autumn: September, October, November; Spring: March, April May; Summer: June, July, August; Winter December, January, February)*

Testing Pattern

Of the total 922 tests prescribed for suspected scrub typhus in the three health centres in Zhemgang, only 8.2 % (n=76) were tested positive. Of these, Yebilaptsa Hospital is observed to have highest number of tests (n=446) followed by Panbang Hospital (n=324) and Zhemgang Hospital (n=152). Panbang Hospital had highest reported positive for scrub typhus with 56.6%(n=43) relative to the number of tests prescribed. Yebilaptsa Hospital had 35.5%(n=27) tests positive while Zhemgang Hospital had 7.9%(n=6). The tests prescribed for scrub typhus was minimal during winter months with December and January months contributing less than 15 tests in all health centres combined. The testing pattern picks up from the month of March and goes peak during the summer months of July through to September as shown in Figure 1.

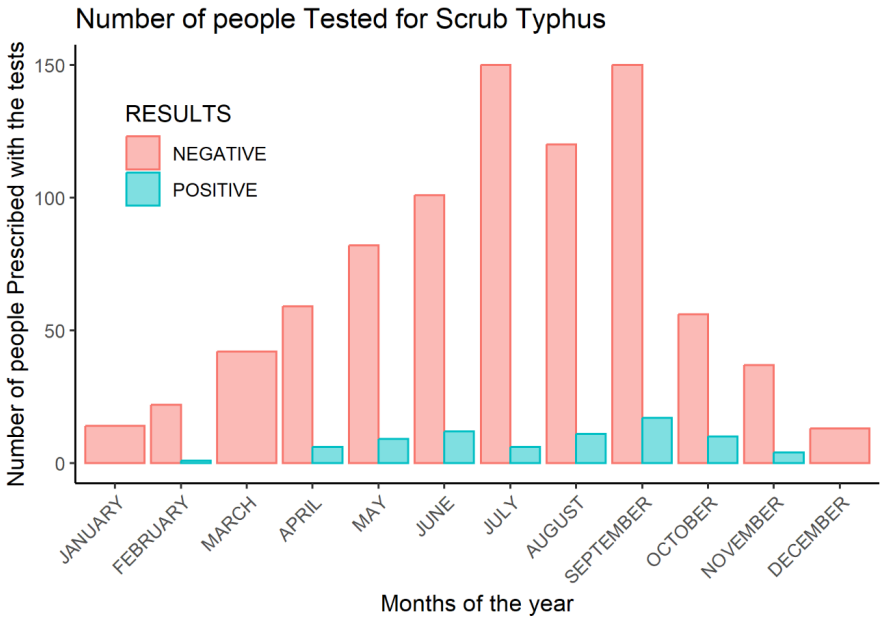

Figure 1Pattern of Scrub Typhus Testing in 3 Health Centres in Zhemgang, 2019-2020

Logistic Regression models were fitted to identify the potential predictors for positive scrub typhus tests from the available variables. We found that the variables are associated with the scrub typhus testing positive. We deduce from the regression that odds of testing positive of scrub typhus is 3 times higher in Panbang Hospital compared to Yebilaptsa Hospital with p value < 0.001 (CI. 1.791 – 5.191).The odds of testing positive if it is Zhemgang Hospital is0.7 times the Yebilaptsa Hospital, however this is statistically shown to be insignificant. Age is shown to be strong predictors for the positive scrub typhus test. For each one-year increase in age, the odds of testing positive for the Scrub typhus increased by 1with p value <0.001 (CI, 1.011 – 1.036). The change of season is not found to be significant predictor for positive scrub typhus testing except for winter months were tests prescribed were negligible. The regression output is provided in table 3.

Table 3 Logistic Regression Output, Pattern of Scrub Typhus Tests in 3 Health Centres in Zhemgang, 2019-2020

	OR	**SE**	**Z**	**p-value**	**95% CI**
(Intercept)	0.039	0.444	-7.277	0.000	(0.017, 0.094)
Zhemgang Hospital	0.738	0.484	-0.627	0.531	(0.286, 1.905)

	OR	SE	Z	p-value	95% CI
Panbang Hospital	3.049	0.271	4.107	0.000	(1.791, 5.191)
AGE	1.024	0.006	3.703	0.000	(1.011, 1.036)
SEX *Male	0.717	0.250	-1.327	0.185	(0.439, 1.172)
Spring	0.794	0.363	-0.635	0.526	(0.390, 1.618)
Summer	0.635	0.360	-1.259	0.208	(0.313, 1.288)
Winter	0.078	1.053	-2.420	0.016	(0.010, 0.616)

Discussion

Our findings suggest that there are over prescription of the test by the physicians. This is truer during the summer and autumn months where tests positive were proportionately low compared to the prescribed number of tests. The female gender is comparably more affected as opposed to male with 57.9% (n=44) of the positive cases being female. Our analysis shows that although the testing pattern differ across the months and seasons, the positive cases of the result are not determined by it. Proportionately, a smaller number of people were tested positive for high number of test prescriptions. The year 2019 noted significant scrub typhus cases accounting to 89.5%(n=68) of the total positive cases over the two years.

Bhutan has environmentally, climatically and occupationally favourable for transmission of scrub typhus infections. Zhemgang is the remotest and the least developed district in the country. In our study, the overall infection rate was 8.2% which is minimal compare to the study conducted in Nepal at Chitwan district in 2016[9]. Panbang Hospital is located in lower altitude compare to Yebilaptsa and Zhemgang Hospital. It is a hot and humid place and share border with Indian state of Assam.A study conducted in Nepal indicate the potential cross-border transmission of scrub typhus infection, which may explain why Panbang has higher positive cases among the three health centres.

Scrub typhus infection is a public health problem in Bhutan. It remained silent after the first casein 2008. Adata-based research from 2009-2014 found that number of positive results increased over the years with the trend of seasons[10]. More female being tested positive in our study concurs with a study conducted in Himalayan region of India[11] and that of Sri Lanka[12]. In rural Bhutan, females usually engaged more farm and livestock works than males which could be a possible explanation for this difference.

The seasonal variation in positive cases, although statistically not a significant predictor was shown to be higher in autumn and summer. Summer and autumn are the seasons for major farm works in rural Bhutan leading to increased exposure for outdoor activities. These are also the months of high rainfall with humid and hot climate compared to other seasons. This could explain the higher prevalence of the disease during these seasons. These findings are concurrent to the study from southern China describing climate variability of the Scrub Typhus[13].

Through the years 2010 to 2014, scrub typhus was reported to be unknown among the health care workers in Bhutan. Our analysis showed high proportions of tests prescribed compared to the positive outcome. Other acutefebrile illnesses such as dengue and other rickettsialdiseasescan cause infectionssimilar to scrub typhus infection[14]. Physicians need to be clearly aware of the disease pathology and diagnosis mechanisms. This way over testing can be prevented and resources well utilized. Awareness of the Scrub Typhus and its diagnoses need to be reinforced. The programmatic approach to disease awareness, disease pathology and disease diagnosis must be reinforced among prescribing physicians. The field implementation must be enhanced in geographically and occupationally high risk of exposure groups.

Limitations

The demographic details of the patients except for the age was not available to in the laboratory registers.Data was available for only 2 years, 2019 – 2020 although greater number of years were considered originally. All the laboratories have conducted the test on two different commercial rapid test kits within two years and such test kits are not the gold standard.

Conclusions

The overall tests tested positive of the scrub typhus infection within two years was 8.2%. We observed huger over prescription of the tests with positive results being proportionately less compared to number of tests prescribed. Prescribers reinforcement training in disease management and awareness among the general public are highly recommended. Geographical areas, demographic determinants and climate determinants maybe of future research interest.

DECLARATIONS

Ethics Approval

Ethics approval was obtained from the Research and Ethics Board of the Ministry of Health, Royal Government of Bhutan, Ref. *No. REBH/Approval/2021/079.* A waiver of consent has been sought from the committee and has been granted based on the study design. All methods were carried out in accordance with relevant guidelines and regulations as enshrined in Helsinki Declarations 1964.

Consent for Publication: Not Applicable

Availability of Data and Materials

Data and materials available from the authors upon request.

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Authors' Contributions

KN: Conception/design acquisition of data, manuscript drafting, giving approval for the final version to be published.

TG: Conception/design of the protocol, data analysis/interpretation, manuscript drafting/critical review of the paper and approval of the final version to be published.

KC & KD: Critically reviewing the paper and giving approval for the final version to be published.

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