



BRIEF REPORT

REVISED Improving the leptospirosis disease burden assessment by including ambulatory patients from outpatient departments: a cross-sectional study [version 2; peer review: 2 approved]

Janith Warnasekara ¹, Parami Aberathna^{1,2}, Geetha Nanayakkara³, Joseph Vinetz⁴, Suneth Agampodi ¹

¹Department of Community Medicine, Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka, Saliyapura, Anuradhapura, 50008, Sri Lanka

²Department of Family Medicine, Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka, Saliyapura, Anuradhapura, 50008, Sri Lanka

³Teaching Hospital Rathnapura, Rathnapura, Sri Lanka

⁴Section of Infectious Diseases, Department of Internal Medicine, School of Medicine, Yale University, New Haven, 208022, USA

v2 First published: 14 Sep 2020, 9:1129
<https://doi.org/10.12688/f1000research.26202.1>

Latest published: 10 May 2021, 9:1129
<https://doi.org/10.12688/f1000research.26202.2>

Abstract

Background: In Sri Lanka, the disease burden of leptospirosis is estimated based on a routine notification system, which is predominated by patients ill enough to be hospitalized. The notification system does not function well with ambulatory patients in outpatient departments (OPDs). The objective of this study was to determine the proportion of leptospirosis in an OPD setting in a regional public hospital in Sri Lanka to provide further estimation of disease burden.

Methods: This study was conducted in the OPD of the Rathnapura Provincial General Hospital from August to September 2017. Suspected leptospirosis patients were recruited based on standardized criteria and tested using the microscopic agglutination test and quantitative polymerase chain reaction. The number of OPD patients was compared with the reported patient numbers with leptospirosis from the hospital during the same period as the denominator, and the 95% confidence interval was calculated for the proportions using Poisson distribution.

Results: During the study period, of 2,960 fever patients presenting to the OPD, 33 (1.1%) were suspected to have leptospirosis; 8/33 suspected (22.3%) cases were confirmed as being due to leptospirosis. There were 82 notifications of leptospirosis cases from hospital inpatients during the same period, none from the OPD. The total missing proportion from the surveillance system was 28.6% (95% CI,

Open Peer Review

Reviewer Status

	Invited Reviewers	
	1	2
version 2		
(revision)		
10 May 2021		report
version 1		
14 Sep 2020	report	report

1. **Georgies F Mgode**, Sokoine University of Agriculture, Morogoro, Tanzania

2. **Chinthika P. Gunasekara** , University of Sri Jayewardenepura, Nugegoda, Sri Lanka

Any reports and responses or comments on the article can be found at the end of the article.

19.4-40.4%). Among OPD patients, 12 (36.4%) had been given antibiotics from a primary care center prior to the OPD visit. No OPD patient was admitted to the hospital for inward care.

Conclusions: More than 25% of cases of leptospirosis were not identified because they were not sick enough to be admitted nor subjected to routine leptospirosis diagnostic testing. These data have public health implications if the sources of leptospirosis transmission are to be controlled.

Keywords

Leptospirosis, Sri Lanka, Outpatient department, Ambulatory care, OPD, burden, underestimation

Corresponding author: Janith Warnasekara (jwarnasekara@yahoo.com)

Author roles: **Warnasekara J:** Conceptualization, Data Curation, Formal Analysis, Methodology, Project Administration, Resources, Writing – Original Draft Preparation, Writing – Review & Editing; **Aberathna P:** Data Curation, Methodology; **Nanayakkara G:** Data Curation, Investigation, Supervision; **Vinetz J:** Conceptualization, Funding Acquisition, Project Administration, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Agampodi S:** Conceptualization, Data Curation, Formal Analysis, Methodology, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This work was partially funded by National Institute of Allergy and Infectious Diseases [U19AI115658]. *The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

Copyright: © 2021 Warnasekara J *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Warnasekara J, Aberathna P, Nanayakkara G *et al.* **Improving the leptospirosis disease burden assessment by including ambulatory patients from outpatient departments: a cross-sectional study [version 2; peer review: 2 approved]** F1000Research 2021, 9:1129 <https://doi.org/10.12688/f1000research.26202.2>

First published: 14 Sep 2020, 9:1129 <https://doi.org/10.12688/f1000research.26202.1>

REVISED Amendments from Version 1

After submitting the first version of the manuscript, we received comments from two reviewers. Both reviewers did an excellent job, and the comments helped to improve the quality of the paper. We made the following major changes to the manuscript. The spelling, grammar, and formatting of the text are revised and corrected. We have added an additional file as extended data for the list of serovars used in the MAT panel to diagnose leptospirosis. Some of the misleading parts of the questionnaire were explained, and the corrected questionnaire is uploaded. There was a mismatch between the abstract and the main text. The abstract mentioned “antibiotics” while it was “treatment” in the main text. We have changed the treatment to “antibiotic treatment” in the results section of the main text. All changes are mentioned as track changes in the manuscript.

Any further responses from the reviewers can be found at the end of the article

Introduction

Assessing the true burden of disease is required for proper health planning and resource allocation, including the control of transmissible diseases such as leptospirosis. Sri Lankan communicable disease burden estimates are usually done using routinely reported data in the surveillance system¹. Lack of actionable diagnostic tests and the diversity of clinical features leading to under-notification of leptospirosis are the major reasons for poor estimation of this disease, a leading cause of acute febrile illness in Sri Lanka^{2,3}. A recently published systematic review has suggested a correction factor for hospitalized leptospirosis cases to estimate the burden of this disease more accurately. This study estimated the incidence of leptospirosis in Sri Lanka as 52.1 per 100,000 population³. However, these estimations and corrections are made for hospitalized patients without considering outpatient departments (OPDs). It is estimated that approximately 5–15% of outpatients with undifferentiated febrile cases could be due to leptospirosis^{4,5}, and undifferentiated febrile patients usually present to OPDs. Finally, these estimates have not been applied to assessing disability-adjusted life years, which is always a challenge for acute febrile illnesses. Therefore, prospective studies in the outpatient setting are essential for estimating the burden of disease due to leptospirosis, which in turn is needed to justify investment in diagnostics and vaccine development.

Few studies have assessed leptospirosis in non-hospitalized patients with acute febrile illness. Biggs *et al.* highlighted the underestimation of leptospirosis due to the non-inclusion of ambulatory patients for disease estimates in Tanzania⁶. A study conducted in Vanuatu showed the importance of screening for leptospirosis among acute febrile illness patients presenting to OPDs during outbreaks, highlighting the need for improved awareness and diagnostic capacity, which are interrelated⁷. In the Vanuatu study, 12 of 161 (7.4%) suspected patients were confirmed as having leptospirosis. However, only 2 of 12 confirmed patients had criteria fulfilling the surveillance case definition, showing the inadequacy of the case definitions used⁷. Another study conducted in Guadeloupe, Martinique (French territories in

the Caribbean) suggested that the actual burden of leptospirosis could be 3 to 4 times higher than reported cases⁸. A study conducted in Mozambique also provided supportive evidence for the importance of outpatient leptospirosis by estimating that as much as 10% of febrile patients attending ambulatory care could be attributed to leptospirosis⁹. The purpose of the present study was to determine the prevalence of leptospirosis in an OPD setting in a regional public hospital in Sri Lanka to provide further estimation of disease burden estimations.

Methods**Setting**

The study was conducted from August 2017 to September 2017 in the OPD of Rathnapura Provincial General Hospital (RPGH) as a part of a larger clinico-epidemiological study. Previous data suggested that the Rathnapura district is one of four major districts affected by leptospirosis¹⁰. At the time of the present study, the OPD had a separate desk for patients presenting with acute febrile illness. This was partly due to the massive epidemic of dengue ongoing during that period.

Participants and data collection

Once the medical officer screened the patients for obvious foci of infection, and after sending probable dengue patients for further investigation, a medical graduate awaiting an internship appointment screened the remaining acute undifferentiated fever patients. Clinically suspected patients were recruited as “possible” cases of leptospirosis using a standardized, written surveillance case definition for Sri Lanka¹¹. In the meantime, a survey was conducted among inward clinically confirmed leptospirosis patients of RPGH to assess the past treatment history.

Recruited patients were interviewed using a standardized, written clinical data checklist and a questionnaire (*Extended data*). A blood sample of 4ml was taken, and 2ml was transferred to a plain tube and 2ml to an EDTA tube and stored in the microbiology laboratory of RPGH.

Samples were transported to the public health research laboratory of the Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka. Testing for leptospirosis was done using the microscopic agglutination test (MAT) and quantitative polymerase chain reaction, as previously published in the study protocol¹².

Hospital notification data were obtained from the infection control unit at RPGH. The number of confirmed OPD patients was compared with the number of leptospirosis-confirmed hospitalized patients during the same period and normalized to total patient populations. Care-seeking was compared with a sample of hospitalized patients treated as leptospirosis by attending physicians.

Data analysis

A SPSS trial version 23 was used for data analysis. A Poisson distribution was used to calculate the 95% confidence interval for the missing patient estimates from OPD.

Ethical considerations

Ethical approval for this research was obtained from the Ethics Review Committee of the Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka (No: ERC/2015/18). Written informed consent was obtained from all the patients for participation in the study.

Results

A total of 2,960 febrile patients were screened in the fever section of the OPD during the study period. Of these, 33 (1.1%) were clinically suspected leptospirosis patients and all were recruited for the present study (Figure 1). These included 23 (69.7%) men and 10 (30.3%) women. The mean age was 46.5 years (SD 17.1). During the same period, RPGH made 82 notifications of possible cases of leptospirosis from hospitalized patients. The missing OPD patients from the notification accounted for 28.6% (95% CI 19.4-40.4) (Table 1).

Of 33 possible cases, 8 (24.2%) were laboratory-confirmed as leptospirosis. One patient was categorized as “probable” with a single MAT titre of 1/200¹². Of the 33 cases selected, 12 (36.4%) had received antibiotic treatment from a primary care centre before coming to the RPGH OPD. During the same period, we interviewed 29 hospitalized patients who were treated presumptively for leptospirosis. Of these, 19 (66.5%) reported that they were given treatment for fever from a primary care provider

prior to hospital admission. However, none of these 19 visited the OPD of RPGH, confirming that the cases presented to OPD are really “missing” from the system.

Discussion

In this preliminary study to evaluate the missing leptospirosis patient load in the surveillance system, we made three important observations: (1) almost one-third of the patients presenting to the OPD of RPGH were missing from the notification system; (2) most of the patients (although we could say none, there might be admissions after the study period) presenting to the OPD were not hospitalized; (3) most of the hospitalized patients sought healthcare from primary care centres rather than from a tertiary care centre. The OPD data clearly shows that 28.6% (95% CI 19.4-40.4) of leptospirosis patients presenting to this tertiary centre were not included in the system. Nevertheless, statistical assumptions cannot be made for the primary care institution without proper studies conducted in local hospitals and private healthcare institutions. This study mainly focused on the cases presenting in an endemic setting and during an outbreak period. The missing numbers can neither be generalized to all areas of Sri Lanka nor for all the months of the year in the same area. Establishing a well-functioning disease surveillance system in OPDs and primary care institutions is essential for proper disease burden estimates, not only for leptospirosis, but also for other

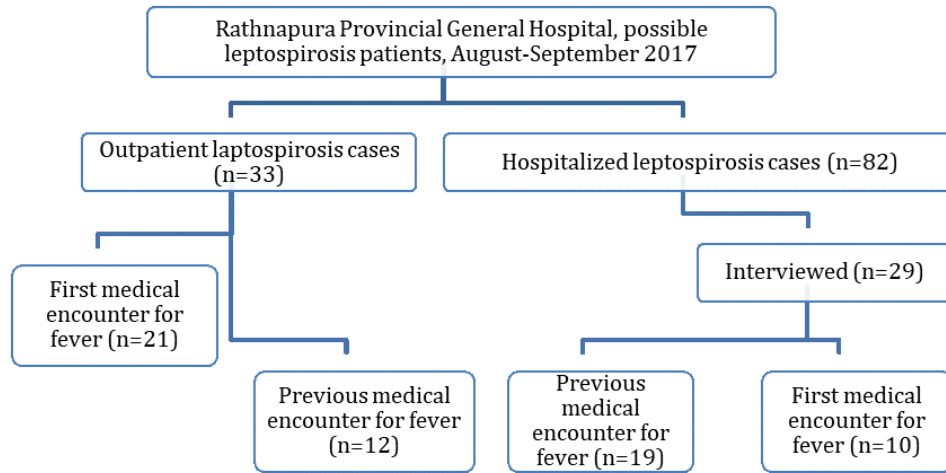


Figure 1. Flow chart of patient selection and diagnosis.

Table 1. Comparison of hospital-reported cases with outpatient department cases.

Month	Total notifications	Notifiable cases from outpatient department	Percentage missing from surveillance system	95%-CI of percentage missing
August	31	11	26.1%	17.7-38.0
September	51	22	30.1%	21.0-42.8
Total	82	33	28.6%	19.4-40.4

notifiable diseases. Various small-scale studies have been conducted to identify feasible methods for disease surveillance, such as incorporating smartphone technology, which is being carried by hand by the treating physician¹³. These feasibility studies need to be upscaled to identify the barriers and feasible methods to implement the system. Well-planned studies covering outpatient, inpatient, and private sectors should be initiated to estimate the actual burden of diseases.

Data availability

Underlying data

Zenodo: OPD Lepto Database - Clinical check List, <http://doi.org/10.5281/zenodo.4013248>¹⁴.

Extended data

Zenodo: OPD Lepto Database - Clinical check List, <http://doi.org/10.5281/zenodo.4013248>¹⁴.

This project contains the following extended data:

- Questionnaire OPD (1st Interview)
- Event calendar
- MAT panel

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

References

1. Epidemiology Unit - Sri Lanka: **Quarterly Epidemiological Report**. Accessed June 27, 2017.
[Reference Source](#)
2. Dahanayaka NJ, Warnasekara YP, Rajapakse RM, *et al.*: **Validity of Lateral Flow Immunochromatographic-Assays (LFIA) in diagnosis of leptospirosis**. *Ceylon Med J.* 2017; **62**(4): 248–49.
[PubMed Abstract](#) | [Publisher Full Text](#)
3. Warnasekara J, Koralegedara I, Agampodi S: **Estimating the burden of leptospirosis in Sri Lanka; a systematic review**. *BMC Infect Dis.* 2019; **19**(1): 119.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
4. Abhilash KPP, Jeevan JA, Mitra S, *et al.*: **Acute undifferentiated febrile illness in patients presenting to a Tertiary Care Hospital in South India: clinical spectrum and outcome**. *J Glob Infect Dis.* 2016; **8**(4): 147–154.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
5. Reller ME, Bodinayake C, Nagahawatte A, *et al.*: **Leptospirosis as frequent cause of acute febrile illness in southern Sri Lanka**. *Emerg Infect Dis.* 2011; **17**(9): 1678–1684.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
6. Biggs HM, Hertz JT, Munishi OM, *et al.*: **Estimating leptospirosis incidence using hospital-based surveillance and a population-based health care utilization survey in Tanzania**. *PLoS Negl Trop Dis.* 2013; **7**(12): e2589.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
7. Pakoa JG, Soupé-Gilbert ME, Girault D, *et al.*: **High incidence of leptospirosis in an observational study of hospital outpatients in Vanuatu highlights the need for improved awareness and diagnostic capacities**. *PLoS Negl Trop Dis.* 2018; **12**(6): e0006564.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
8. Cassadou S, Rosine J, Flamand C, *et al.*: **Underestimation of leptospirosis Incidence in the French West Indies**. Foley J ed. *PLoS Negl Trop Dis.* 2016; **10**(4): e0004668.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
9. Collares-Pereira M, Gomes AC, Prasad M, *et al.*: **Preliminary survey of Leptospirosis and Lyme disease amongst febrile patients attending community hospital ambulatory care in Maputo, Mozambique**. *Cent Afr J Med.* 1997; **43**(8): 234–238. Accessed October 13, 2019.
[PubMed Abstract](#)
10. Warnasekara JN, Agampodi S: **Leptospirosis in Sri Lanka**. *Sri Lankan J Infect Dis.* 2017; **7**(2): 67.
[Publisher Full Text](#)
11. Agampodi S: **Case definitions in Leptospirosis: a note to Sri Lankan researchers**. *Sri Lankan J Infect Dis.* 2012; **2**(2): 55–57.
[Publisher Full Text](#)
12. Agampodi S, Warnasekara J, Jayasundara D, *et al.*: **Study protocol: characterising the clinical, epidemiological and aetiological aspects of leptospirosis in Sri Lanka: a hospital based clinico-epidemiological study**. *BMJ Open.* 2019; **9**(9): e027850.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
13. Warnasekara YPJN, Agampodi SB, Marage PM, *et al.*: **Real time surveillance of dengue fever – a preliminary study**. *Ceylon Med J.* 2016; **61**(4): 197–198.
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Warnasekara J, Agampodi S: **OPD Lepto Data base - Clinical check List**. Zenodo. 2020.
<http://www.doi.org/10.5281/zenodo.4013248>

Open Peer Review

Current Peer Review Status:  

Version 2

Reviewer Report 24 May 2021

<https://doi.org/10.5256/f1000research.56435.r85002>

© 2021 Gunasekara C. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Chinthika P. Gunasekara 

Department of Microbiology, University of Sri Jayewardenepura, Nugegoda, Sri Lanka

I have gone through the revisions and the article is now acceptable for indexing.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 19 April 2021

<https://doi.org/10.5256/f1000research.28916.r82774>

© 2021 Gunasekara C. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Chinthika P. Gunasekara 

Department of Microbiology, University of Sri Jayewardenepura, Nugegoda, Sri Lanka

In this study the authors address an important aspect of leptospirosis burden in Sri Lanka that is a timely need. The main finding of the study that is conducted in a high prevalent district Rathnapura is that the true burden of leptospirosis is underestimated and about 28% cases coming to the OPD for treatment are not reported.

I suggest that the authors include more recent references including data from the epidemiological unit as there are several publications done in Sri Lanka published more recently.

The supporting files are missing some components as the part C of the questionnaire. Further the abstract results section mentions some data that is not described by way of table, additional data or described in the results section and this should be corrected to support the findings and conclusion. for example antibiotic history.

There are several spelling errors Eg : plane tube - plain tube. Overall I believe that the results section should be slightly expanded to support the conclusions and findings. This is an interesting paper and I recommend it for indexing subject to revision.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Leptospirosis, immune response

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 24 Apr 2021

Janith Warnasekara, Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka, Saliyapura, Sri Lanka

Comment

I suggest that the authors include more recent references including data from the epidemiological unit as there are several publications done in Sri Lanka published more recently.

Reply

This was submitted as a **brief report** with a specific focus and the reference included were only directly related to the narrow focus. This was the reason for having a small results section. Extensive discussions on all Sri Lankan publications were done as a part of the larger study, which has included epidemiological unit data and data from all recent papers. (Published systematic review DOI: 10.1186/s12879-018-3655-y 6364467)

Comment

The supporting files are missing some components as the part C of the questionnaire.

Reply

Yes. We understand that some of the phrases in questionnaire are misleading. This study was conducted as a part of large clinical study related to leptospirosis. The Part C and further sections were for inward patients (not relevant to this brief report). We only applied Part A and B for OPD patients as the duration of interview with an OPD patient is less than the inward patients. To avoid misinterpretation, misleading parts were explained in the questionnaire. Corrected questionnaire is uploaded as extended data.

Eg: Go to part C (Only the inward Patients)

Comment

Further the abstract results section mentions some data that is not described by way of table, additional data or described in the results section and this should be corrected to support the findings and conclusion. for example antibiotic history.

Reply

First part of the results section of the abstract was explained in the figure one and the rest is in the table.

We identify that 12 patients received antibiotics are mentioned as "antibiotics" in the abstract and as "treatment" in the main text.

To avoid misinterpretation, we have changed the treatment as "antibiotic treatment" in the main text results section.

Comment

There are several spelling errors Eg: plane tube - plain tube.

Reply

Spelling, grammar and formatting of the text are revised and corrected. All changes are mentioned as track changes in the manuscript.

Comment

Overall I believe that the results section should be slightly expanded to support the conclusions and findings.

Reply

We humbly agree that the results section is small. As explained earlier, this is a brief report with very specific focus and we have included all the data relevant to this aim in this paper.

Competing Interests: No competing interests were disclosed.

Reviewer Report 10 February 2021

<https://doi.org/10.5256/f1000research.28916.r74988>

© 2021 Mgode G. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Georgies F Mgode

Pest Management Centre, Sokoine University of Agriculture, Morogoro, Tanzania

The authors present important findings on leptospirosis from outpatients population. It is a well designed study and covered a large sample size consisting of 2,960 individuals with febrile illness.

- In the methodology section: plane tube should be "plain tube".
- Further description of the microscopic agglutination test (MAT) is needed given that it is a core test for confirmation of leptospirosis. Information on *Leptospira* serovars used, age and whether was live or killed is much needed.

Recommendation to establish a well-functioning disease surveillance system is important.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Rodent borne zoonotic diseases - leptospirosis and plague disease, tuberculosis and taxonomy

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 10 Feb 2021

Janith Warnasekara, Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka, Saliyapura, Sri Lanka

Thank you very much for the response. I agree with the comments made by the reviewer. I would like to do the following changes in the manuscript.

1. Change the plane into plain in methodology
2. Add a supplementary file of full MAT protocol

Thank you very much

Competing Interests: No Competing interests

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research