PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Establishing a sentinel surveillance system for the novel coronavirus disease 2019 (COVID-19) in a resource limited county: methods, system attributes and early findings
AUTHORS	Das, Pritimoy; Akhtar, Zubair; Mah-E-Muneer, Syeda; Islam, Md.; Rahman, Mohammed; Rahman, Mustafizur; Rahman, Mahmudur; Rahman, Mahbubur; Billah, Mallick; Alamgir, A. S. M; Flora, Meerjady Sabrina; Shirin, Tahmina; Banu, Sayera; Chowdhury, Fahmida

VERSION 1 – REVIEW

REVIEWER	Kretchy, James-Paul Central University, Public Health
REVIEW RETURNED	20-Jul-2021

GENERAL COMMENTS	**REVIEW COMMENTS FOR THE MANUSCRIPT TITLED, "ESTABLISHING A SENTINEL SURVEILLANCE SYSTEM FOR THE NOVEL CORONAVIRUS DISEASE 2019 (COVID-19) IN A RESOURCE LIMITED COUNTY: METHODS, SYSTEM ATTRIBUTES AND EARLY FINDINGS"** **Reviewer's general comment:** The authors conducted an interesting study on methods, system attributes and early findings on establishing a sentinel surveillance system for COVID-19 in a resource limited county in Bangladesh. Taken together, this research was systematically conducted with sound ethical principles. The discussion and conclusions were based on the findings for which reasons I recommend its acceptance and publication subject to the authors' responses to the below comments. Abstract i. Begin the introduction with a more global perspective of the topic. Remove abbreviations in opening statements and throughout abstract. ii. Report prevalence values as n (%) throughout. iii. "Diabetic patients were more likely to get COVID-19 than non-diabetic (48% vs. 38%, p<0.05)". Indicate the odds ratio and confidence intervals. Introduction i. Consider adding a concluding paragraph with the aim / s of the study clearly stated ii. Replace "it's" in line 31, page 4 with 'its' iii. "The government of Bangladesh (GoB) initiated several efforts for the early detection of the virus to

		mitigate the spread: screening of passengers at airports, land ports, and maritime ports; hotline system to notify any suspected case of COVID-19 to the Institute of….." remove colon and replace with 'such as'
	Methods	
	i.	The selection and classification criteria for the 4 hospitals as secondary and tertiary has to be clarified
	ii.	Indicate the relative locations of the selected hospitals by GPS
	iii.	Were there no RT-PCR facilities at the only private tertiary hospital? How was this hospital classified as tertiary?
	iv.	"Selected hospitals were three public and one private hospital situated in different geographical locations across Bangladesh (Figure 1). These were three secondary level government hospitals (Sadar Hospital, Hobiganj, General Hospital, Potuakhali, District Hospital, Narshingdi) and one tertiary level private medical college hospital (Jahurul Islam Medical College hospital, Kishoregonj). To select these hospitals, we identified national Influenza surveillance/hospital-based Influenza surveillance sites, where there was no nearby polymerase chain reaction (PCR) test facility but a high load of potential suspected COVID-19 patients". Please summarize here and make it read clearer.
	v.	Patient case-definition must be explained further, removed from parenthesis and referenced.
	vi.	Limit the use of personal and second-person pronouns in methods and data analysis sections
	vii.	Replace the section on 'data collection' with 'patient enrollment' and vice-versa.
	viii.	"After obtaining written informed consent from those who met the suspected COVID-19 case definition"…. How many met the inclusion criteria?
	ix.	"our staff collected data on socio-demographics, travel history, and clinical characteristics from them.." who were these staff and how many were they?
	x.	How different were surveillance staff from field staff, how many were in each category?
	xi.	Enlist the specific PPE used by the surveillance staff. Did they need to use PPE also in the follow-ups?
	xii.	Provide detailed description of how the nasopharyngeal swab were collected and from how many patients. Were all the samples used in the analysis? How many samples were excluded from the analysis and for what reasons?
	xiii.	State the manufacturer details of VTM
	xiv.	Replace "at 2-4 degree °C temperature" to between "2-4 degree °C temperature"
	xv.	At what time in the evening did the porter transport the specimen? Is the porter a field or surveillance staff? By what means were the samples transported and within approximately how many hours / minutes did the samples reach the laboratory for analysis?
	xvi.	"RNA was tested for SARS-CoV-2 by"… begin statements with written-out abbreviations

	xvii. "We used univariate regression analysis for the interpretation of the outcome variable". Provide further explanations to this statement and add detail to the data analysis section. For example, you tested for strengths of associations and identified risk factors, using odds ratios xviii. Authors should state the ethical clearance number, how they ensured confidentiality / anonymity and how they obtained permission from the hospital authorities before data collection Results i. Consistently report percentages as n (%) throughout ii. Results section must be segregated into sub-sections. For example provide separate sub-sections for text description on each of the Tables or supplementary information provided. The current presentation looks disorderly. Discussion i. Limit the discussion to explanations of your key findings. There seems to be several repetitions of results in the discussion. ii. Authors should include findings from other related studies from elsewhere to make their discussion more informative. For example, there are several referral details in this literature that might be considered by the authors; "Ibrahim, N.K., 2020. Epidemiologic surveillance for controlling Covid-19 pandemic: challenges and implications. Journal of infection and public health". Conclusion i. "Though a small initiative, our COVID-19 sentinel surveillance revealed many key findings for the policymakers to understand this pandemic in the country context". This statement is not clear and can be removed. ii. How did the risk factor associations translate into any conclusion to this study and how can these be used to advise policy makers in the study context? References i. Kindly check from the author guidelines and follow the approved reference style. List of Tables i. Add a column of logistic regression in Table 2 and indicate the adjusted and unadjusted odds ratios. It is not clear whether the current odds ratios in the Table are adjusted or raw.

REVIEWER	Kretchy, Irene School of Pharmacy, University of Ghana, Department of Pharmacy Practice and Clinical Pharmacy
REVIEW RETURNED	24-Jul-2021

GENERAL COMMENTS	REVIEW COMMENT

	TITLE: Establishing a Sentinel Surveillance System for the Novel Coronavirus Disease 2019 (COVID-19) in a Resource Limited County: Methods, System Attributes and Early Findings Abstract • The concluding statement should derive from the findings • Re-arrange key words alphabetically Introduction • "To support the containment efforts for COVID-19, International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)…." Use 'the' in front of 'International' • Use referenced information on page 5. Methods • State the study variables and which were dependent and outcome variables. How did you control for confounders. • Indicate the ethical clearance number. State whether permission was obtained from the healthcare facilities used in data collection. • How did you ensure anonymity of study participants and confidentiality of the information provided • I do not understand the section on "Patient and public involvement". Is this adding anything new? Results • The authors should revise the section on results and present them in a more clear and coherent way. • The percentages should be preceded by the frequencies [i.e. n (%)]. Discussion The discussions seem to be heavy on repetition of the results. This should be corrected and have the discussions more focused on providing explanations for main findings in line or otherwise with related studies in literature.

VERSION 1 – AUTHOR RESPONSE

RESPONSE TO REVIEWER-1

Abstract

• The concluding statement should derive from the findings

Response: We have updated the conclusion section based on our findings in page 2: "COVID-19 positivity was observed in more than one-third of suspected COVID-19 patients attending selected hospitals. While managing such patients, the risk factors identified for higher death rates should be considered."

• Re-arrange key words alphabetically

Response: We have rearranged keywords alphabetically according to the suggestion in page 2 as "Bangladesh, COVID-19, hospital-based study, SARS-CoV-2, sentinel surveillance".

Introduction

• "To support the containment efforts for COVID-19, International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)…." Use 'the' in front of 'International'

Response: We have updated the sentence and used 'the' in front of both the organizations in page 6.

• Use referenced information on page 5.

Response: In page 5, we have added more references (reference number 14, 15, 16 and 17) in this paragraph to support our statements.

Methods

• State the study variables and which were dependent and outcome variables. How did you control for confounders.

Response: The study variables are now elaborated in greater detail in the manuscript, and language has been added to explain how we adjusted for them, as shown below:

Page no 7-8: "Field staff collected data on socio-demographics (age, sex, occupation, educational level), travel history (local or international travel), and clinical characteristics (presenting symptoms, clinical signs, comorbidity, admission status, smoking history, duration of symptom onset to treatment seeking) from them… The outcome variables were COVID-19 positivity by RT-PCR test and the mortality among the SARS-CoV-2 infected patients." In page no. 9: "… We used univariate logistic regression analysis for strengths of associations and identified risk factors for death, using odds ratios and adjusted for age and sex in the multivariable model."

• Indicate the ethical clearance number. State whether permission was obtained from the healthcare facilities used in data collection.

Response: Added the ethical clearance number PR-20032 in page 10. Yes, necessary permission was obtained from the respective hospitals before establishing the hospital-based platform and data collection (added in page 9).

• How did you ensure anonymity of study participants and confidentiality of the information provided

Response: To ensure anonymity of the study participants and maintain the confidentiality, the names and identifying information of the participants was and will not be shared with anyone outside of the data collection team and this information was kept in locked cabinets and/or computers with passwords. Laboratory specimens were identified only by patient enrolment ID. The code that links a study number to patient's name was kept by principal investigator in locked files. They were not associated with specimens sent to the laboratory. Presentations of the data in public forums or in scientific reports will not report the name or identifying information of any patient. Our institutional Ethical Committee reviewed the study protocol and consent form before final approval. We added this in page 9 under the ***Ethical consideration.***

• I do not understand the section on "Patient and public involvement". Is this adding anything new?

Response: For the BMJOpen journal, this is a required section. On page 10, we've revised the language to make this section clearer: "Patients or the public were not involved in the study design, or conduct, or reporting, or dissemination plans."

Results

• The authors should revise the section on results and present them in a more clear and coherent way.

Response: Thanks for the suggestion. We have revised the result section and added sub-heading for better understanding of findings related to a specific analysis, page number 10-12.

• The percentages should be preceded by the frequencies [i.e. n (%)].

Response: We have added frequencies along with % throughout the updated result section.

Discussion

The discussions seem to be heavy on repetition of the results. This should be corrected and have the discussions more focused on providing explanations for main findings in line or otherwise with related studies in literature.

Response: We agree. We have carefully revised the discussion section taking into account the valuable suggestions of the reviewer. We strongly believe that current discussion is more focused and provided comparison/contrast/ explanations of our main findings and provided major limitation of our study (page 12-17).

RESPONSE TO REVIEWER-2

Reviewer's general comment: The authors conducted an interesting study on methods, system attributes and early findings on establishing a sentinel surveillance system for COVID-19 in a resource limited county in Bangladesh. Taken together, this research was systematically conducted with sound ethical principles. The discussion and conclusions were based on the findings for which reasons I recommend its acceptance and publication subject to the authors' responses to the below comments.

Abstract

i. Begin the introduction with a more global perspective of the topic. Remove abbreviations in opening statements and throughout abstract.

Response: Thanks for your kind review and valuable feedback in the manuscript. We have changed the full abstract as per the suggestion from the editor into a new format excluding the introduction section. We have removed all abbreviations at the first time used in abstract and other parts of the manuscript accordingly.

ii. Report prevalence values as n (%) throughout.

Response: We have updated all results with frequency and percentage in the result section (page 10-12) and other area of the manuscript where applicable.

iii. "Diabetic patients were more likely to get COVID-19 than non-diabetic (48%vs. 38%,

p<0.05)". Indicate the odds ratio and confidence intervals.

Response: The change is reflected in page no 2: "Diabetic patients were more likely to get COVID-19 than non-diabetic (OR:1.5; 95% CI: 1.2-1.9)."

Introduction

i. Consider adding a concluding paragraph with the aim / s of the study clearly stated

Response: We have added the following sentence at the end of the concluding paragraph to mention the study objective in page no 6: "The aim of this study was to establish a hospital-based platform with limited resources to describe and analyze epidemiological and clinical characteristics of patients screened for COVID-19 in Bangladeshi hospitals during the early months of the pandemic."

ii. Replace "it's" in line 31, page 4 with 'its'

Response: It has been changed to its from it's.

iii. "The government of Bangladesh (GoB) initiated several efforts for the early detection of the virus to mitigate the spread: screening of passengers at airports, land ports, and maritime ports; hotline system to notify any suspected case of COVID-19 to the Institute of….." remove colon and replace with 'such as'

Response: We have removed colon (:) and replaced with 'such as' as suggested in page no 4.

Methods

i. The selection and classification criteria for the 4 hospitals as secondary and tertiary has to be clarified

Response: The section has been revised for more clarity as suggested in page number 6 as"The surveillance was conducted at the outpatient department (OPD) and inpatient department (IPD) of four selected hospitals where patients sought healthcare with suspected COVID-19 symptoms. There were three public hospitals and one private hospital, all of which were in different geographical locations across Bangladesh (Figure 1). The public hospitals namely Sadar Hospital, Hobiganj (24°22'24.77", 91°25'3.62"), General Hospital, Potuakhali (22°21'52.19", 90°19'37.25" and, District Hospital, Narshingdi (23°55' 48.6", 90°42' 9.84"), all having 100-250 number of beds. Jahurul Islam Medical College hospital, Kishoregonj (24°12' 2.26", 90°55'1.81") is a general tertiary level 500 bed teaching hospital. To select these hospitals, we evaluated the ongoing national hospital-based Influenza surveillance platforms to identify the hospitals where there was no in-hospital or nearby polymerase chain reaction (PCR) based COVID-19 testing facility at that time but a high load of potential suspected COVID-19 patients in that geographical location. It was considered that additional support to these hospitals would

strengthen COVID-19 case identification and reporting at the national level with generation of epidemiological data."

ii. Indicate the relative locations of the selected hospitals by GPS

Response: GPS location is now added for each hospital in page 6 (please see above)

iii. Were there no RT-PCR facilities at the only private tertiary hospital? How was this hospital classified as tertiary?

Response: There were just a few government-approved PCR facilities that could test for COVID-19 at the time and none of our selected hospitals including the private hospital had the COVID-19 testing facility and we have incorporated this in our protocol in page 6-7 as "To select these hospitals, … no in-hospital or nearby polymerase chain reaction (PCR) based COVID-19 testing facility…." . The private hospital, Jahurul Islam medical college hospital is a 500-bed medical college teaching hospital with all essential departments and acted as a referral hospital for district and subdistrict hospitals of the catchment area.

iv. "Selected hospitals were three public and one private hospital situated in different geographical locations across Bangladesh (Figure 1). These were three secondary level government hospitals (Sadar Hospital, Hobiganj, General Hospital, Potuakhali, District Hospital, Narshingdi) and one tertiary level private medical college hospital (Jahurul Islam Medical College hospital, Kishoregonj). To select these hospitals, we identified national Influenza surveillance/hospital-based Influenza surveillance sites, where there was no nearby polymerase chain reaction (PCR) test facility but a high load of potential suspected COVID-19 patients". Please summarize here and make it read clearer.

Response: We have revised the study setting section as suggested for better understanding in page no. 6 and 7.

v. Patient case-definition must be explained further, removed from parenthesis and referenced.

Response: As suggested, case definition used in this surveillance has been explained clearly in page number 8 as "Case definition for screening: patient with any one or more of the following symptoms within last 7 days- fever, cough, sore throat, and respiratory distress." We have removed the case-definition from the parenthesis and this case-definition was defined by GoB, so we could not use any standard reference.

vi. Limit the use of personal and second-person pronouns in methods and data analysis sections

Response: Thank you for the suggestion. We have used specific word such as 'field staff' and removed 'we/our' from the manuscript where appropriate.

vii. Replace the section on 'data collection' with 'patient enrollment' and vice-versa.

Response: We respect your thought; however, we still think that the "data collection" and "patient enrolment" sub-heading was properly reflecting the underlying paragraphs.

viii. "After obtaining written informed consent from those who met the suspected COVID-19 case definition"…. How many met the inclusion criteria?

Response: During the reporting period, all 2345 patients reported in result section met the inclusion criteria and was enrolled in the study. As these patients were seeking healthcare at hospitals and were willing to test for COVID-19, which was free of cost from our study, everyone was included in this study.

ix. "our staff collected data on socio-demographics, travel history, and clinical characteristics from them.." who were these staff and how many were they?

x. Response: As suggested we have added the numbers of field staffs in page 7 as "we deployed two trained field staff in each selected hospital (total eight field staff placed in four hospitals) for screening…..".How different were surveillance staff from field staff, how many were in each category?

Response to (ix) and (x): Apologies for any confusion caused by the use of both field and surveillance staff. All surveillance hospitals received a total of eight field staff, having two field staff assigned to each facility. In page numbers 7-8, we removed the 'surveillance staff' from the manuscript and replaced it with the 'filed staff.'

xi. Enlist the specific PPE used by the surveillance staff. Did they need to use PPE also in the follow-ups?

Response: We have added "Field staff used proper personal protective equipment (PPE) such as N95 mask/medical mask, disposable gown, disposable cap, disposable gloves, face shield and goggles during data and specimen collection" in page no 7. As the follow-ups were taken by telephone interview, no PPE were used.

xii. Provide detailed description of how the nasopharyngeal swab were collected and from how many patients. Were all the samples used in the analysis? How many samples were excluded from the analysis and for what reasons?

Response: We have provided detailed description of the sample collection, transportation and testing in the manuscript as suggested in specimen collection and transportation and laboratory testing section in page 8 and 9.

We collected nasopharyngeal swab samples from all the enrolled patients and all the samples were considered in analysis as none of the samples were excluded. For better clarification in page no. 10 we have incorporated: "Virology Laboratory of icddr,b tested all the 2,345 nasopharyngeal swab samples collected from those enrolled participants; of them, 922 (39.3%) were laboratory-confirmed COVID-19 patients."

xiii. State the manufacturer details of VTM

Response: As suggested we have added in page 8 "Inhouse (icddr,b lab) VTM preparation was used for the collected samples" (Added in page number 8). VTM was consist of basic tissue culture medium supplemented with 2.5% (v/v) bovine serum albumin, fraction V (Invitrogen) and 0.8% (v/v) fungizone (Invitrogen). The basic tissue culture medium was consist of Dulbecco's modified eagle medium (DMEM) (Invitrogen) supplemented with 2.0%

(v/v) HEPES (Invitrogen), 1.0% (v/v) L-Glutamate (Invitrogen), 1.0% (v/v) Penicillin-Streptomycin (Invitrogen), 1.0% (v/v) Sodium Pyruvate and 3.7 g/L Sodium bicarbonate. The pH of the VTM preparation was set at 7.4. After preparation, it was filtered using 0.22 µm syringe filter. An aliquot of VTM was kept in a CO_2 incubator at 37°C for two weeks to check for any contamination. We did not provide this level of details as we consider this may distract focus of the manuscript.

xiv. Replace “at 2-4 degree °C temperature” to between “2-4 degree °C temperature”

Response: Replaced accordingly in page no-8.

xv. At what time in the evening did the porter transport the specimen? Is the porter a field or surveillance staff? By what means were the samples transported and within approximately how many hours / minutes did the samples reach the laboratory for analysis?

Response: Answer to these queries were now mentioned in page number 8: “. Every afternoon, a dedicated porter transported all the samples to icddr,b, Dhaka using a private car from three surveillance hospitals except Patuakhali. From Patuakhali, one of the dedicated porter brought samples to icddr,b by launch (public transport). All VTMs were handed over to icddr,b laboratory within 24 hours of specimen collection.”

xvi. “RNA was tested for SARS-CoV-2 by”… begin statements with written-out abbreviations

Response: Replaced accordingly in page no 9 as “Riboneucleic acid (RNA) was extracted from nasopharyngeal swab using QiaAmp Viral RNA Mini kit (Qiagen, Hilden, Germany). RNA was tested for Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)…”

xvii. “We used univariate regression analysis for the interpretation of the outcome variable”. Provide further explanations to this statement and add detail to the data analysis section. For example, you tested for strengths of associations and identified risk factors, using odds ratios

Response: Thanks for highlighting this. We have updated the data analysis section in page number 9 as “… We used univariate logistic regression analysis for strengths of associations and identified risk factors for death, using odds ratio for the interpretation of the outcome variable and adjusted for age and sex in the multivariable model.”

xviii. Authors should state the ethical clearance number, how they ensured confidentiality / anonymity and how they obtained permission from the hospital authorities before data collection

Response: We have added the ethical clearance number PR-20032 in page 9. To ensure anonymity of the study participants and maintain the confidentiality, the names and identifying information of the participants was and will not be shared with anyone outside of the data collection team and this information was kept in locked cabinets and/or computers with passwords. Laboratory specimens were identified only by patient enrolment ID. The code that links a study number to patient’s name was kept by principal

investigator in locked files. They were not associated with specimens sent to the laboratory. Presentations of the data in public forums or in scientific reports will not report the name or identifying information of any patient. Our institutional Ethical Committee reviewed the study protocol and consent form before final approval. We have briefly mentioned this in the ethics section of the updated manuscript (page 9).

Results

i. Consistently report percentages as n (%) throughout

Response: We have added frequencies along with % throughout the updated result section, page number 10-12.

ii. Results section must be segregated into sub-sections. For example provide separate sub-sections for text description on each of the Tables or supplementary information provided. The current presentation looks disorderly.

Response: Thanks for the suggestion. We have revised the result section and added sub-heading for better understanding of findings related to a specific analysis, page number 10-12.

Discussion

i. Limit the discussion to explanations of your key findings. There seems to be several repetitions of results in the discussion.

ii. Authors should include findings from other related studies from elsewhere to make their discussion more informative. For example, there are several referral details in this literature that might be considered by the authors; “Ibrahim, N.K., 2020. Epidemiologic surveillance for controlling Covid-19 pandemic: challenges and implications. Journal of infection and public health”.

Response: We agree with the concern raised by the respected reviewer. We have carefully revised the discussion section considering the valuable suggestions of the reviewer. We strongly believe that current discussion is more focused and provided comparison/contrast/ explanations of our main findings and provided major limitation of our study (page 12-17).

Again, we have added more references and cited studies as per the recommendation in page number 5-6.

Conclusion

i. “Though a small initiative, our COVID-19 sentinel surveillance revealed many key findings for the policymakers to understand this pandemic in the country context”. This statement is not clear and can be removed.

Response: We agree. As suggested, we have removed the statement from the conclusion.

ii. How did the risk factor associations translate into any conclusion to this study and

how can these be used to advise policy makers in the study context?

Response: Policymakers may consider a system for the early identification of the COVID-19 positive individuals at high risk to provide special care with time-appropriate treatment. (Page number 17).

References

i. Kindly check from the author guidelines and follow the approved reference style.
Response: Thanks for notifying this. We have updated the reference style.

List of Tables

i. Add a column of logistic regression in Table 2 and indicate the adjusted and unadjusted odds ratios. It is not clear whether the current odds ratios in the Table are adjusted or raw.
Response: Thanks for the valuable feedback. As suggested, we have added the adjusted odds ratio in a column and updated Table 2 in page number 25.

VERSION 2 – REVIEW

REVIEWER	Kretchy, James-Paul Central University, Public Health
REVIEW RETURNED	11-Oct-2021

GENERAL COMMENTS	Please include female information under the demographic variable sex, in Table 1.

VERSION 2 – AUTHOR RESPONSE

RESPONSE TO REVIEWER-1

Reviewer: 1
Dr. James-Paul Kretchy, Central University, Central University, Ghana
Comments to the Author:
Please include female information under the demographic variable sex, in Table 1.

Response: Thank you for your kind suggestion and comments for the improvement of this manuscript. In the revised table, we have now added another row to include female information in Table 1 (Page number 24) as below:

Characteristics		Suspected COVID-19 patients (N=2345)	SARS-CoV-2 Positive by rRT-PCR		
			Total Positive (922)	Inpatient (57)	Out-patient (865)
				n (%)	n (%)
Sex					
	Male	1590 (67.8)	654 (70.9)	38 (66.7)	616 (71.2)
	Female	755 (32.2)	268 (29.1)	19 (33.3)	249 (28.8)