PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Epidemiologic Investigation of the First 5,685 Cases of SARS-CoV-2 Infection in Qatar, February 28-April 18, 2020
AUTHORS	Al Kuwari, Hanan; Abdul Rahim, Hanan; Abu-Raddad, Laith; Abou-Samra, Abdul-Badi; Al Kanaani, Zaina; Al Khal, Abdullatif; Al Kuwari, Einas; Al Marri, salih; Al Masalmani, Muna; Al Romaihi, Hamad; Al Thani, Mohammed; Coyle, Peter; Latif, Ali; Owen, Robert; Bertollini, Roberto; Butt, Adeel

VERSION 1 – REVIEW

REVIEWER	Thuong V Nguyen Pasteur Institute Ho Chi Minh City Vietnam
REVIEW RETURNED	12-Jul-2020

GENERAL COMMENTS	In general, it is an interesting paper about the COVID-19 outbreak with a large sample size. The authors gave an initial epidemiological picture of COVID-19 in Qatar. However, several points should be addressed as per following: 1. The method was not clear how to address the epidemiologic curve as described in the objectives 2. For the outcome of disease, asymptomatic should be separated with minimal symptoms to see what is the percentage of the asymptomatic COVID-19. 3. The age of disease is rather important. It is better the Authors describe the age in median, range besides partitioning the age into different groups. Age of 0-20 should be separated 0-10, 11-15, 16-.... to see what is going on with the children 4. In analysis, variables of "hypertension" and "cardiovascular diseases" were put together in the model. These 2 variables may have high correlation, causing high collinearity, which may cause at least some regression coefficients to have the wrong sign. 5. For the nationality, why did the authors not classify by the ethnics. 6. In the abstract: for the design, I would say "case series" rather than epidemiologic investigation which may use different epidemiologic designs (cases series, cross-sectional study, cohort,....) 7. With the current study methods, it is hard to assess the impact of public health measures on the covid-19

REVIEWER	Suliman Khan The Second Affiliated Hospital of Zhengzhou University, China
REVIEW RETURNED	06-Aug-2020

GENERAL COMMENTS	This paper requires further modifications or revisions so that it could be published in a scientific journal. Please revise according to the following suggestions 1. Please re-read carefully and remove all the repeating sentences and unnecessary details. 2. Revise for grammatical and technical mistakes. The writing style is more like an essay for a magazine rather than a scientific journal. 3. This paper in its current form does not add anything new to the already available data. Please add more details regarding the treatment and recovery of the patients included. 4. I think the authors should further investigate the death rate, recovery rate, recovery of patients who were on a ventilator, Medications, preventive measures, and precautions considered by the healthcare authorities. 5. Revise the discussion section for a comparison of the data with the recently published data from other countries. Discuss if there is any difference in recovery and death rate? If yes, please discuss the possible reasons.

REVIEWER	Samuel J. Stratton, MD, MPH University of California, Los Angeles USA
REVIEW RETURNED	16-Aug-2020

GENERAL COMMENTS	GENERAL COMMENTS: I appreciate the opportunity to review this interesting epidemiological study. SPECIFIC COMMENTS: 1.Introduction: A more concise and specific study objective is suggested. This is a COVID-19 epidemiological study of a predominately young adult male population that is mainly expatriates in a developed region of western Asia. 2. Introduction: It is noted that many of those who reside in Qatar are expatriates. Helpful would be to describe the freedom that these individuals had for travel into and outside of Qatar during the study period. 3. Methods: Please state the technique used for population testing. It appears that testing was not done on random samples of the population, rather purposeful sampling (based on presence of influenza-like symptoms or severe acute respiratory infection) was used. To represent the entire population of Qatar, testing on a random basis (random cluster analysis most feasible) and without selection bias (all residents had the same probability to be tested) is required. 4. Methods: Please report the manufacturer established sensitivity and specificity for the type of RT-PCR testing used. 5. Please explain the criteria used to determine a “close contact” for a positive COVID case. 6. Results: Google mobility section, please provide data for travel into and out of Qatar.

	7. Discussion: The discussion of the limitations of the study should include the study not employing random sampling and that testing results may have included false positives and false negatives. 8. Conclusion: The conclusion statement should be qualified by stating that “for the population tested, the pandemic …”. As noted above, the study cannot apply to the entire population of Qatar due to the non-probability sampling method. 9. Table 4: consider stating in the Conclusion that important findings of the study were that hypertension and diabetes mellitus, but not age were associated with severe illness.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name

Thuong V Nguyen

Institution and Country

Pasteur Institute Ho Chi Minh City

Vietnam

Please state any competing interests or state ‘None declared’:

None declared

In general, it is an interesting paper about the COVID-19 outbreak with a large sample size. The authors gave an initial epidemiological picture of COVID-19 in Qatar. However, several points should be addressed as per following:

1. The method was not clear how to address the epidemiologic curve as described in the objectives

RESPONSE: We retrospectively identified all patients with a confirmed COVID-19 diagnosis from the Ministry of Public Health database, which monitors and tracks every diagnosed patient in the country. We retrieved demographic and clinical data from the electronic health records of each patient. Nationality was ascertained from the official State Identification Card. We have added details of data collection and methodology to the revised version.

2. For the outcome of disease, asymptomatic should be separated with minimal symptoms to see what is the percentage of the asymptomatic COVID-19.

RESPONSE: The reviewer makes a good point. However, we did not differentiate between asymptomatic or minimally symptomatic persons in the original study. Based on our observations and extensive published data, there are no differences in clinical outcomes between asymptomatic or minimally symptomatic persons. Mild symptoms may progress to more severe disease, and this has been captured in our data. Furthermore, this distinction is often difficult to make unless "asymptomatic" patients are followed closely for some time, as some may later report mild symptoms.

3. The age of disease is rather important. It is better the Authors describe the age in median, range besides partitioning the age into different groups. Age of 0-20 should be separated 0-10, 11-15, 16-....

to see what is going on with the children

RESPONSE: Thank you for this suggestion. We looked at age with multiple different groupings and ranges. Among those aged 0-10, only 3 out of 121 children had mild upper respiratory symptoms without evidence of pneumonia; all others were asymptomatic. Among those aged 11-15, none of the 44 children were symptomatic. Among those aged 16-18, 1 had mild upper respiratory symptoms without evidence of pneumonia and 2 had severe disease. There were no incidences of critical illness and no deaths in children. These numbers were too low for each of those age categories to be entered into a regression model, therefore we grouped ages 0-20 together. However, if the reviewer prefers to add the descriptive information in the manuscript, this can be done.

4. In analysis, variables of "hypertension" and "cardiovascular diseases" were put together in the model. These 2 variables may have high correlation, causing high collinearity, which may cause at least some regression coefficients to have the wrong sign.

RESPONSE: We fully agree with the reviewer that collinearity may exist between hypertension and CVD. However, we checked for this and found no collinearity between these variables. The diagnostics are provided below:

Collinearity Diagnostics					
Number	Eigenvalue	Condition Index	Proportion of Variation		
			Intercept	Hyper	CVD
1	1.87295	1.00000	0.06591	0.10399	0.10303
2	0.86824	1.46873	0.92236	0.02389	0.04669

3	0.25881	2.69013	0.01173	0.87211	0.85028

5. For the nationality, why did the authors not classify by the ethnics.

RESPONSE: We do not gather ethnicity data in the State of Qatar in any of our databases.

6. In the abstract: for the design, I would say "case series" rather than epidemiologic investigation which may use different epidemiologic designs (cases series, cross-sectional study, cohort,....)

RESPONSE: Thank you for this excellent suggestion. We have modified this in the revised draft.

7. With the current study methods, it is hard to assess the impact of public health measures on the covid-19

RESPONSE: The reviewer makes a very valid point. It is extremely difficult to make any causal inferences in a case series. We have been careful not to assign any causality to the public health measures. However, it is important to indicate when those measures were implemented so that the readers can get a full picture of how the pandemic evolved in Qatar. We have removed this objective from the list of stated objectives to avoid any confusion.

Reviewer: 2

Reviewer Name

Suliman Khan

Institution and Country

The Second Affiliated Hospital of Zhengzhou University, China

Please state any competing interests or state ‘None declared’:

None declared

This paper requires further modifications or revisions so that it could be published in a scientific journal. Please revise according to the following suggestions

1. Please re-read carefully and remove all the repeating sentences and unnecessary details.

RESPONSE: We thank the reviewer for carefully reading our paper and providing this feedback. We have carefully re-read the paper and removed repeating sentences.

2. Revise for grammatical and technical mistakes. The writing style is more like an essay for a magazine rather than a scientific journal.

RESPONSE: Once again, we thank the reviewer for carefully reading our paper and providing this feedback. We have carefully re-read the paper to remove any grammatical and technical mistakes.

3. This paper in its current form does not add anything new to the already available data. Please add more details regarding the treatment and recovery of the patients included.

RESPONSE: The reviewer raises an important point. At the time of writing this report, enough follow-up was not available to accurately determine outcomes. Since then, more data have become available and are the subject of a separate publication from Qatar by another team of investigators. Briefly, the first 5,000 patients were followed up for up to 60 days after diagnosis of COVID-19. By that time, a total of 1,424 patients (28.5%) required hospitalization, out of which 108 (7.6%) were admitted to ICU. 14 patients (0.28%) had died, 10 (0.2%) were still in hospital, and two (0.04%) were still in ICU. We have added these data and the appropriate reference (non-peer reviewed but available on a pre-print server) to the revised manuscript.

4. I think the authors should further investigate the death rate, recovery rate, recovery of patients who were on a ventilator, Medications, preventive measures, and precautions considered by the healthcare authorities.

RESPONSE: This is another important point which has been addressed in another publication focusing on clinical data. Our paper was written as an urgent public health response to define the early epidemiologic features. We have provided the reference to the other paper and a brief summary of some of those results.

5. Revise the discussion section for a comparison of the data with the recently published data from other countries. Discuss if there is any difference in recovery and death rate? If yes, please discuss the possible reasons.

RESPONSE: Thank you for this excellent suggestion. We have added a full paragraph in the discussion section to address this.

Reviewer: 3

Reviewer Name

Samuel J. Stratton, MD, MPH

Institution and Country

University of California, Los Angeles

USA

Please state any competing interests or state 'None declared':

None

GENERAL COMMENTS:

I appreciate the opportunity to review this interesting epidemiological study.

RESPONSE: Thank you for reviewing our paper.

SPECIFIC COMMENTS:

1.Introduction: A more concise and specific study objective is suggested. This is a COVID-19 epidemiological study of a predominately young adult male population that is mainly expatriates in a developed region of western Asia.

RESPONSE: Thank you for this suggestion. We have added a statement in the introduction to reflect this.

2. Introduction: It is noted that many of those who reside in Qatar are expatriates. Helpful would be to describe the freedom that these individuals had for travel into and outside of Qatar during the study period.

RESPONSE: Thank you for this suggestion. We have added this information in the introduction as suggested by the reviewer. Briefly, there were no travel restrictions in the early part of the study, i.e. from February 28 to March 30, 2020. A general restriction on all incoming flights into Qatar was implemented on March 31, which halted almost all influx of visitors or residents into the country. Exit travel was not generally restricted. However, two factors diminished outbound travel sharply: 1) global restrictions on travel leading to a sharp reduction in all flights; 2) restriction of essential workers from taking leave and travelling except in urgent or emergency situations. As can be expected, exact numbers are not available, but airline volumes and airport entry/exit transactions reflect these realities.

3. Methods: Please state the technique used for population testing. It appears that testing was not done on random samples of the population, rather purposeful sampling (based on presence of influenza-like symptoms or severe acute respiratory infection) was used. To represent the entire population of Qatar, testing on a random basis (random cluster analysis most feasible) and without selection bias (all residents had the same probability to be tested) is required.

RESPONSE: We fully agree with the reviewer and have added this to the revised manuscript. We would like to point out that (1) the purpose of the study was not to estimate prevalence/incidence, for which a probability-based representative sample is more critical, and (2) it reflected the testing strategy at that stage of the epidemic, which has since evolved.

4. Methods: Please report the manufacturer established sensitivity and specificity for the type of RT-PCR testing used.

RESPONSE: Despite extensive search, there are no available data on the exact sensitivity and specificity of the RT-PCR tests used. In clinical settings, sensitivity of PCR is highly dependent on the type of specimen, method of collection and transport and timing of specimen collection in relation to the course of illness. These are all factors that determine the presence and amount of virus in the specimen delivered to the lab. If viral genomic materials are present, then the sensitivity of RT-PCR approaches 100%. Specificity is similarly determined by factors related to specimen collection and viral load and not as much on test characteristics. We have briefly mentioned this in the revised manuscript.

5. Please explain the criteria used to determine a “close contact” for a positive COVID case.

RESPONSE: Close contacts were identified based on US CDC criteria which define a close contact as "any individual who was within 6 feet of an infected person for at least 15 minutes starting from 2 days before illness onset (or, for asymptomatic patients, 2 days prior to positive specimen collection) until the time the patient is isolated." We have added this to the revised manuscript.

6. Results: Google mobility section, please provide data for travel into and out of Qatar.

RESPONSE: Unfortunately these data are not available to us at this time.

7. Discussion: The discussion of the limitations of the study should include the study not employing random sampling and that testing results may have included false positives and false negatives.

RESPONSE: Thank you for pointing out this important limitation which has been added to the revised manuscript.

8. Conclusion: The conclusion statement should be qualified by stating that "for the population tested, the pandemic …". As noted above, the study cannot apply to the entire population of Qatar due to the non-probability sampling method.

RESPONSE: Thank you for pointing out this important distinction. We have added this to the revised manuscript.

9. Table 4: consider stating in the Conclusion that important findings of the study were that hypertension and diabetes mellitus, but not age were associated with severe illness.

RESPONSE: Thank you for this comment. We have added this to the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Suliman Khan The second Affiliated hospital of Zhengzhou University, PR China
REVIEW RETURNED	01-Sep-2020

GENERAL COMMENTS	The previous comments have been answered but there are several grammatical mistakes in the revised manuscript. I suggest the authors to revise carefully for grammatical mistakes. I was unable to find clean word file, and I cannot enlist all the changes

	needed here. For example some sentences can be corrected as "in residential, The presence of hypertension, having a severe, with the presence, admission to acute care or an intensive care bed, Changes in population movement were assessed", and so on. Please update the references, some recent studies can be cited such papers published by Khan et al. in saudi pharmaceutical journal.

REVIEWER	Samuel J. Stratton, MD, MPH University of California, Los Angeles USA
REVIEW RETURNED	29-Aug-2020

GENERAL COMMENTS	Thank you for the opportunity to review this revised manuscript. My concerns and questions submitted for the original manuscript have been addressed within this revision.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 3

Reviewer Name

Samuel J. Stratton, MD, MPH

Institution and Country

University of California, Los Angeles

USA

Please state any competing interests or state ‘None declared’:

None

Please leave your comments for the authors below Thank you for the opportunity to review this revised manuscript. My concerns and questions submitted for the original manuscript have been addressed within this revision.

RESPONSE: Thank you for your previous comments and for reviewing our paper again.

Reviewer: 2

Reviewer Name

Suliman Khan

Institution and Country

The second Affiliated hospital of Zhengzhou University, PR China

Please state any competing interests or state ‘None declared’:

None declared

Please leave your comments for the authors below The previous comments have been answered but there are several grammatical mistakes in the revised manuscript. I suggest the authors to revise carefully for grammatical mistakes. I was unable to find clean word file, and I cannot enlist all the changes needed here. For example some sentences can be corrected as "in residential, The presence of hypertension, having a severe, with the presence, admission to acute care or an intensive care bed, Changes in population movement were assessed", and so on.

RESPONSE: We have carefully read the manuscript and corrected any minor errors. The manuscript has been read by native English speakers to ensure accuracy.

Please update the references, some recent studies can be cited such papers published by Khan et al. in saudi pharmaceutical journal.

RESPONSE: We thank the reviewer for this suggestion. We respectfully submit that the paper mentioned by the reviewer (for which the reviewer is the first author) described a new pharmacologic treatment agent in a very small and limited population. This has not been validated in larger clinical trials. Furthermore, our paper is an epidemiologic study and not a treatment study. Therefore we feel that this citation is not suitable for our paper.