Author's response to reviews

Title: A comparative epidemiologic analysis of SARS in Hong Kong, Beijing and Taiwan

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Author's response to reviews: see over

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Melissa Norton
Editor-in-Chief
BMC Infectious Diseases

Dear Dr Norton,

Re: A comparative epidemiologic analysis of SARS in Hong Kong, Beijing and Taiwan

We thank the editor and reviewers for their helpful comments, which have allowed us to improve our manuscript. Of particular note, we have clarified the approval, source and definition of the data, and revised the Background section of the abstract. Our detailed responses to the reviewers' comments are given below.

Looking forward to your further comments on the paper.

On behalf of all authors,
Yours sincerely,

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Associate Editor comments:

The authors should precise the case-definition and sources of data (particularly as regards Beijing data).

We have now clarified in the Methods section the case definition and sources of data. In particular, when we conducted data extraction in Beijing we also reviewed the clinical presentation, exposure history, blood test, chest CT and X-ray of the patients in additional to WHO definitions. This is now clarified in the Methods section.

They should give greater details on which variables were used to adjust odds-ratio.

We have now clarified in the Methods section the variables which were used to adjust odds-ratio. We also added footnotes to state all the variables adjusted in each of the table with adjusted odds ratio.

Editorial requests:

- Please revise the Background section of your Abstract to include additional context information in addition to aims.

We have now included additional context in the Background section of the Abstract, which now reads:

"The 2002-2003 Severe Acute Respiratory Syndrome (SARS) outbreak infected 8,422 individuals leading to 916 deaths around the world. However, there have been few epidemiological studies of SARS comparing epidemiologic features across regions. The aim of this study is to identify similarities and differences in SARS epidemiology in three populations with similar host and viral genotype."

- Please clarify approval for the use of the data.

Approval for the use of the Hong Kong data was obtained from the Hong Kong Department of Health, under a collaborative agreement that has led to a number of other papers (e.g. Leung et al. Ann Int Med). Approval for the use of the Taiwan data was obtained from Taiwan CDC. Approval for the use of the Beijing data were obtained from the medical directors of the 301 (XTS), 302 and 309 hospitals included in our study. Ethical approval was obtained from the relevant authorities in each location. This project was supported by the EU-funded SARSTRANS consortium, which coordinated collection and sharing of data across the 3 regions.

Reviewer 1 comment

General: This paper aims to examine risk factors across three major populations who experienced the SARS outbreak. It is an excellent idea as it provides power to the analyses. In the main this is an excellent paper but I would like to several major issues to be considered by the authors to strengthen the paper.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Methods.
• The Beijing data were redefined in a 2007 publication (Liang et al Public health 2007 Oct;121(10):725-33) according to the WHO definition with 2443 cases reduced to 1862 cases with age, sex, residential, date onset or admission etc.

Q1. Do the 917 cases used in this paper fulfil the WHO case definition?

The 917 cases satisfied the WHO case definition. However, the Beijing health officials also reviewed clinical presentation, exposure history, blood test, chest CT and X-ray scan for the probable cases. We have now clarified the definitions of the Beijing probable cases on page 7, paragraph 2, line 4, which reads:

"In Beijing, clinical presentation, exposure history, blood test, chest CT and X-ray scan were also reviewed in additional to the WHO definition."

If this cannot be achieved please indicate in your methods the change in the number of cases (Liang et al 2007) this limitation to your dataset.

In our dataset and in Liang's paper, there is not enough information to compare the changes in the number of cases. We have added the following sentence to the limitations:

"Furthermore, while SARS patients in Beijing were classified according to the WHO definition, but a more recent detailed case review has found that some reported 'probable' SARS cases may have been misclassified [44]."

• In the Methods section the source of Beijing and Taiwan data is not explicit.

Taiwan data were collected by the Taiwan CDC, through standardized screening questionnaires at emergency rooms and on admission, as officially documented by the Centers for Disease Control, Taiwan. Beijing data were extracted from chart review of reported 'probable' SARS cases. We have clarified the source of the Beijing and Taiwan data in the methods section.

Q2. Can the authors include in the Methods section the source of the Beijing and Taiwan data?

We have now clarified the source of Beijing and Taiwan data in the Methods section on page 8, line 5 and in the last paragraph, which reads:

"Clinical information was reviewed by a panel of experts in the earlier stage of the epidemics and

furthermore a standardized report form was used after May as previously described [15]. Data were extracted by detailed chart review in each hospital following a standard protocol."

"Similarly, we captured the corresponding data from all 664 probable cases in Taiwan who provided the information through standardized screening questionnaires at emergency rooms and on admission. Data were collected from all hospitals and integrated into a dataset officially maintained by the Centers for Disease Control, Taiwan."

• The authors have stratified their tables by three geographic region assuming that the data within each region is not confounded by

(i) method of acquisition or
(ii) time of acquisition.

(i) In Hong Kong the epidemic was introduced into the community by the index case (AA) but then the outbreak differed with a large proportion of cases being acquired occupationally and environmentally. The authors have already considered healthcare workers (i.e. occupational acquisition) as a potential confounder. But the effect of the other method of acquisition (environmental) may also be a confounder. 18% of cases acquired SARS from the Amoy Garden environmental outbreak from the index case (YY). YY was potentially discharged from hospital on 19th March (with SARS) and experienced diarrhoea at Amoy Gardens 19th March with the majority of the subsequent cases presenting with diarrhoea (66%) and other signs/symptoms between March 24-26, 6-11 days (mode at March 24) after YY experience diarrhoea in his brother's apartment. This could suggest there had been a change in presentation of the disease, duration of disease and possibly the incubation period etc.

Q3. Is Amoy Garden acquisition a confounder and if so alter the tables to include this?

We agree with the reviewer that Amoy Garden acquisition may have been a confounder in terms of disease presentation and possibly fatality. We rerun a multivariable logistic regression model in Hong Kong including Amoy Garden acquisition as an explanatory variable. The result is as follow:

	Hong Kong (n=1755)			
Characteristic	No. of patients (%)*	CFR (%)	AOR† (95% CI)	
Sex				
Female	978 (56)	13.2	1	
Male	777 (44)	22.3	1.40	(1.01-1.94)
Age group (years)				
0-30	515 (29)	0.6	0.05	(0.01-0.18)
31-40	379 (22)	7.1	0.68	(0.38-1.20)
41-50	320 (18)	11.6	1	
51-60	170 (10)	17.6	1.46	(0.83-2.60)
60+	371 (21)	55.3	5.63	(3.52-9.01)
Health Care Worker				
No	1350 (77)	21.8	1	
Yes	405 (23)	2.0	0.26	(0.12-0.59)
Preexisting comorbid conditions				
No	1395 (80)	10.0	1	

Yes	358 (20)	45.5	1.59	(1.09-2.31)
Admitted before symptom onset				
No	1636 (93)	14.6	1	
Yes	119 (6.8)	52.9	1.45	(0.88-2.38)
Amoy Garden acquisition				
No	1418 (81)	12.5	1	
Yes	335 (19)	18.3	1.43	(0.90-2.27)
Deaths / Crude CFR (95% CI)	302	17.2 (15.4, 19.0)		

Furthermore, we fit another logistic regression model including the interactions between Amoy Garden acquisition and all other variables, which all were found to be insignificant. In view of the main focus of the study, to compare the association of the common variables among the three regions with case fatality, and the lack of significantly heterogeneous epidemiological effects on fatality, Amoy Garden acquisition was not included in the model.

(ii) The three Beijing hospitals represent patients from different stages of the epidemic (hosp 309 – early phase with a CFR of 12.5% for patients with rapid onset of symptoms; hosp 302 April onwards CFR 6.1% and XTS Hosp may onwards CFR 1.2% for patients with rapid onset of symptoms).

Q4. It was not clear whether the authors have controlled for hospital when presenting Beijing data as an aggregate?

We agree with the reviewer that there were differences between hospitals. The SARS patients in Hospital 309 were not included in the logistic regression analysis for Beijing, since we did not have information on co-morbid conditions for patients in that hospital. We also refit a logistic regression analysis to test for any differential effects of sex, age, health care worker status, pre-existing co-morbid conditions and nosocomial acquisition between Hospital 302 and XTS Hospital. All the interaction effects were found to be insignificant. In view of the main focus of the study, to compare the association of the common variables among the three regions, hospital effect was not included in the analysis.

In table 1 legend, we now clarified that hospital was not controlled for by stating all the adjusted variables.

• The titles of the tables suggest the odds ratios were adjust. Which variables each geographic location controlled for is not clear as hospital acquired SARS (admitted before symptom onset) was a significant risk factor for Taiwan.

Q5. Please change OR to AOR and list in the Methods section the variable controlled for as well as at the foot of the tables clarifying where a variable was controlled for in one location but not another.

All "OR" were now changed to "AOR" in the main text and in all tables. We also clarified in the table footnotes and in addition file table footnotes the variables controlled in the model. We now state the variables controlled in the multivariable logistic regression model, in the Methods section

on page 9, line 8, which reads:

"We fitted multivariable logistic regression models, controlled for variables such as sex, age, health care worker status, preexisting comorbid conditions and nosocomial infection, for each region on all data allowing us to estimate the adjusted odds ratios of mortality between regions."

• In the tables the authors have used 41-50 years of age as the reference group with neither the highest or the lowest CFR

Q6. Please include for the readers in the Methods section the rationale for this choice?

The main reason of choosing 41-50-year age group as the reference group is to avoid extremely large or small values in the presentation of the adjusted odds ratios. We have now included the rationale in the method section on page 9, line 14, which reads:

"To avoid extreme values in the adjusted odds ratio for the age effect, we chose the middle age group as the reference group"

• Results for incubation period is given as 95th percentile

Q7. Can the authors also provide 25th, 50th and 75th percentiles in the text?

We have now added the 25^{th}, 50^{th} and 75^{th} percentiles for the estimated incubation period on page 12, line 4, which reads:

"The 25, 50, 75 and 95^{th} percentiles were 2, 3, 5 and 12 days in Hong Kong, 1, 3, 6 and 20 days in Beijing and 3, 5, 9 and 18 days in Taiwan."

I would appreciate leaving a review of the Discussion until the authors have considered Q1,3,4.

We look forward to further comments on the manuscript.

Reviewer 2 Comments

This paper analyzes the major epidemiological parameters about the SARS with a very large sample. The results of the research improve the current epidemiological knowledge on the SARS. I have some minor revisions regarding this paper:

1. Pages 7-8: in this study, the 917 patients in Beijing issue from 2521 SARS patients studied in Ref. 15 where the SARS case definition used was not the WHO definition. Did the 3 hospitals in Beijing use the WHO definition?

The definitions were close but not exactly the same as WHO definitions. We have now clarified the definitions of the Beijing probable cases on page 7, paragraph 2, line 4, which reads:

"In Beijing, clinical presentation, exposure history, blood test, chest CT and X-ray scan were also reviewed in additional to the WHO definition."

2. Page 8: what is the difference between "health care worker" and "HCW status"?

Both terms refer to the same group, we now clarified by rewriting the sentence on page 9, line 2, which reads:

"We compared the characteristics of SARS patients by region in terms of demographic variables such as age, sex and health care worker (HCW) status, presence of pre-existing co-morbid conditions (including ischemic heart disease, cerebrovascular…"

3. Page 15, lines 2-3: "However, discounting the highly selected XTS Hospital sample and adjusting for age and sex, the Beijing CFR approximated that of Hong Kong." The results supporting this conclusion should be shown in section "Results".

We now added the adjusted odds ratio in the results section on page 11, line 5 from the bottom, which reads:

"When the XTS Hospital patients were excluded, the adjusted odds ratios (95% confidence intervals) of case fatality for Beijing was 0.98 (0.46 to 2.09) compared to Hong Kong."

4. Table 1: – the footnote "*" is unclear: the patients with missing data were not really excluded; the % was always counted with 3336 patients as the denominator.

We have recalculated the % in Table 1 which now uses the non-missing data as the denominator.

– it is unclear for which variables were adjusted the OR, this could be indicated in the legends of the table.

We now added a legend under Table 1 clarifying the variables which were adjusted, which reads:

"Adjusted for sex, age, health care worker status, preexisting comorbid conditions and nosocomial infection."

– please explain why the 41-50-year age group was defined as the reference group.

The main reason of choosing 41-50-year age group as the reference group is to avoid extremely large or small values in the presentation of the adjusted odds ratios.

5. Table 2: it is unclear for which variables were adjusted the OR, this could be indicated in the legends of the table.

We now added a legend under Table 2 clarifying the variables which were adjusted, which reads:

"Adjusted for sex, age, health care worker status, preexisting comorbid conditions, nosocomial infection and region."

6. Additional files 3&4: – it is unclear for which variables were adjusted the OR, this could be indicated in the legends of the table.

We now added in the original legend in Additional files 3 & 4 the following sentence clarifying the variables which were adjusted:

"Adjusted for sex, age, health care worker status, preexisting comorbid conditions, nosocomial infection and region."

– please provide more details about the test of the interaction effects between the variables.

We now added in the original legend in Additional files 3 & 4 that the Wald test was used, which now reads:

"… also adjusted for significant interaction (based on Wald test) between location with health care worker and pre-existing co-morbid conditions."

7. The paper by Karlberg J. et al (Am J Epidemiol, 2004, 159(3): 229-231) supports this study. It should be referenced and discussed.

We have now included the paper by Karlberg J. et al in the discussion, which reads:

"Male sex was significantly associated with increased risk of fatality in Hong Kong after adjustment

for other important confounding factors, consistent with a previous study in Hong Kong that identified a sex effect in unadjusted analyses of aggregate data [30].”