

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Rapid Increase of Gonorrhoea Cases in Guangdong Province, China, 2014-2017: A Review of Surveillance Data
AUTHORS	Wang, Cheng; Tang, Weiming; Zhao, Peizhen; Tucker, Joseph; Chen, Lei; Smith., M. Kumi; Wong, Ngai Sze; Dong, Willa; Yang, Bin; zheng, heping

VERSION 1 – REVIEW

REVIEWER	Aziza BENNANI Ministry of Health National AIDS Program Manager Morocco
REVIEW RETURNED	17-Jun-2019

GENERAL COMMENTS	I think that results are confusing, since the authors compare two periods (2014-2016) and (2014- 2016) This should be analysed separately and mention the purpose of this comparison and explain the added value of the two periods
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REVIEWER	Martina Furegato - Programme Manager and Epidemiology Lead St. George's, University of London London United Kingdom
REVIEW RETURNED	19-Jun-2019

GENERAL COMMENTS	<p>This is an interesting piece of work exploring the increase in gonorrhoea cases in the region of Guangdong in China in recent years. It includes multiple sources of data to obtain an overall picture of the situation and the trends experienced. However, more work is required to better explain and to investigate whether the data presented are sufficient to evaluate the increase of cases and the impacts on gonorrhoea prevalence.</p> <p>Overall</p> <ul style="list-style-type: none">- It would be very helpful to have the manuscript checked by an English native speaker as the current version is not always easy to follow.- Please amend the spelling of gonorrhoea throughout the manuscript and also I prefer the use of Sexually Transmitted Infections rather than Diseases- Please be rigorous with the statistical analysis performed and include more explanation on how some measures were defined and derived <p>Introduction</p>
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	<ul style="list-style-type: none"> - Page 3, Line 25: Please expand on high incidence of gonorrhoea - Page 3, Lines 31-32: I agree on the association between gonorrhoea and HIV acquisition but I would like you to expand more on the concept of gonorrhoea and transmission of HIV - Page 3, Line 49: please explain why you think that the level un unsafe sex increased in recent years - Page 4, Lines 14-15: please rephrase, too colloquial - Page 4, lines 14-19: this statement should be placed elsewhere as this is linked to the high number of cases reported - Page 5: Statistical analysis: As the methods was divided into the different sources of data, I would suggest to apply the same concept for the description of the statistical analysis - Page 5, line 32: in selecting the 4 hospitals with the highest incidence it might generate biased data. Please also explain why this number of hospital - Page 6, line 15: What is the definition of the new gonorrhoea cases? - Page 6, line 22: how many years were included in this formula? - Page 6, line 24: was a check of the distribution of the data performed to decide to use chi-square test? - There are several other measures included in the results section that have not been defined in the stats section. Please amend accordingly <p>Results</p> <ul style="list-style-type: none"> - Across all the results section, please report a statistical significance when presenting data from different years or from different methods - Page 6, line 42: was a statistical method use to understand whether the mate-to-female ratio decreased from 2014 to 2017 - Page 6, lines 49-57: Please explain why in 2017 other cities were included. - Page 7, line 10: is the 'average yearly' the annual increase in percentage? - Page 7, line 15: please rephrase this, it is not clear to me the meaning. Do you mean that the smear test has been the most used in the past four years? - Page 8, lines 33-34: please define incidence rate - Page 8, line 33-36: the results are not statistically significant for neither syphilis nor chlamydia. <p>Discussion</p> <ul style="list-style-type: none"> - Page 9, lines 35-42: please rephrase as it is not clear the concept you want to convey. - I am not sure if with the data presented you were able to discount from all the biases (more sensitive diagnostics and expanded coverage) there is still a "real" increase in gonorrhoea cases in the region of interest - Page 9, lines 58-60: this is more a conclusion point rather than a discussion point. - Page 10, lines 14-16: please expand on the Zero Mark-up Drug policy and its efficacy and impact on the increase of gonorrhoea cases - Page 10, line 19-20: please include a reference for the work mentioned in brackets.
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	<ul style="list-style-type: none"> - Page 10 ,line 24: The reference 29 included at the end of this paragraphs refers to a study done in Africa so I am not sure if this is relevant with the point expressed in the paragraph - Page 10, lines 37-39: This statement is not clear to me. Are you suggesting that because of an increase in high risk sex behaviours there was an actual increase in the number of gonorrhoea cases? However the sentinel study didn't confirm this findings. In addition, I would suggest to add a multivariable analysis to take this into account, adjusting for the sex behavioural information. - Page 10, line 46: please rephrase this concept. As far as I understood it is difficult to prove that the number of cases are underestimate or not and also please expand on why you think that this is not affecting the trend of incidence for gonorrhoea. <p>Page 1 -18: the supplementary figures don't have titles and descriptions</p>
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VERSION 1 – AUTHOR RESPONSE

Response to reviewer #1

Comment 1: I think that results are confusing, since the authors compare two periods (2014-2016) and (2014- 2016). This should be analyzed separately and mention the purpose of this comparison and explain the added value of the two periods.

Response: Thanks for the reviewer's suggestion. In this study, the focus was to analyze the potential driving forces on the increasing epidemic of gonorrhoea in Guangdong Province between 2014 and 2017. In order to show that the reported incidence of gonorrhoea increased rapidly between 2014 and 2017, we described the epidemic of reported incidence of gonorrhoea between 2004 and 2013 based on the data from the STI CRS, which showed a decreasing trend (see the first paragraph of the Results). Afterwards, we analyzed two additional sources of data which were collected from 2014 to 2017 to explore potential driving forces on the increasing epidemic between 2014 and 2017. Therefore, in this study, our focus was to analyze epidemic data between 2014 and 2017. We have revised the Methods and Results section to clarify for readers.

Response to reviewer #2

Comment 1: It would be very helpful to have the manuscript checked by an English native speaker as the current version is not always easy to follow.

Response: Thanks for the reviewer's suggestion. One of our study team members, Willa Dong, has reviewed the manuscript to ensure the quality of language.

Comment 2: Please amend the spelling of gonorrhoea throughout the manuscript and also I prefer the use of Sexually Transmitted Infections rather than Diseases.

Response: Thanks for the reviewer's reminder and suggestion. We have amended the spelling of gonorrhoea and used the phrase "Sexually Transmitted Infections" instead of "Sexually Transmitted Diseases" throughout the manuscript.

Comment 3: Please be rigorous with the statistical analysis performed and include more explanation on how some measures were defined and derived.

Response: We appreciate the reviewer's suggestion. We have adjusted the statistical analysis performed in this study, provided additional explanations on how some measures were defined and

derived, and added a multivariable analysis to examine the factors associated with gonorrhoea infection in the revised manuscript (see the Statistical analysis of the Methods and the Results section).

Comment 4: Page 3, Line 25: Please expand on high incidence of gonorrhoea.

Response: Thanks for the reviewer's suggestion. We have expanded on the high incidence of gonorrhoea globally in the revised manuscript (see the first paragraph of the Introduction). The World Health Organization (WHO) estimated that in 2012, there were 78 million cases among adults aged 15-49 years worldwide with a global incidence rate of 19 per 1000 females and 24 per 1000 males.[a]

[a]Newman L, Rowley J, Vander HS, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. Plos One 2015; 10(12): e0143304.

Comment 5: Page 3, Lines 31-32: I agree on the association between gonorrhoea and HIV acquisition but I would like you to expand more on the concept of gonorrhoea and transmission of HIV.

Response: Thanks for the reviewer's suggestion. We have added more details on the association between gonorrhoea and HIV acquisition in the Introduction (see the first paragraph of the Introduction). Briefly, gonorrhoea infection can induce the production of cytokines, chemokines and defensins, which can modulate HIV infection and infectivity. [b]

[b]Jarvis GA, Chang TL. Modulation of HIV transmission by Neisseria gonorrhoeae: molecular and immunological aspects. Curr HIV Res 2012; 10(3): 211-7.

Comment 6: Page 3, Line 49: please explain why you think that the level unsafe sex increased in recent years.

Response: Thanks for the reviewer's suggestion. We mentioned that high levels of unsafe sexual behavior among certain subpopulations were considered to be a likely contributor in the manuscript. But this does not mean the unsafe sexual behavior increased in recent years. For example, a serial cross-sectional study conducted by Chinese Center for Disease Control and Prevention[c] showed that the proportion of consistent condom use during anal sex in the last six months increased gradually among Chinese men who have sex with men (MSM) between 2009 and 2014 (from 40.4% to 48.8%, $P < 0.01$). However, around half of MSM still did not consistently use condoms in China. The high level of unsafe sexual behavior may increase the burden of gonorrhoea. We have added more references to support this point (see the second paragraph of the Introduction).

[c] Qin Q, Tang W, Ge L, et al. Changing trend of HIV, Syphilis and Hepatitis C among Men Who Have Sex with Men in China. Scientific Reports 2016; 6: 31081.

[d] Paz-Bailey G, Mendoza MCB, Finlayson T, et al. Trends in condom use among MSM in the United States: the role of antiretroviral therapy and seroadaptive strategies. AIDS (London, England) 2016; 30(12): 1985-90.

Comment 7 and comment 8: Page 4, Lines 14-15: please rephrase, too colloquial. Lines 14-19: this statement should be placed elsewhere as this is linked to the high number of cases reported

Response: Thanks for the reviewer's suggestion. We have rephrased the sentences of lines 14-15 as "Additionally, Guangdong has the most complete and effective surveillance system for STIs among all the provinces in China". Also, we removed the sentences within lines 13-14 from the Introduction since this content has been described in the Results (see the third paragraph of the Introduction, and first paragraph of the Results).

Comment 9: Statistical analysis: As the methods was divided into the different sources of data, I would suggest to apply the same concept for the description of the statistical analysis.

Response: Thanks for the reviewer's suggestion. We have divided the descriptions of the statistical analysis by three different sources of data (see the statistical analysis subsection of the Methods).

Comment 10: Page 5, line 32: in selecting the 4 hospitals with the highest incidence it might generate biased data. Please also explain why this number of hospital

Response: Thanks for the reviewer's suggestion. We have added more information on why and how those hospitals were selected in this study in the revised manuscript (see the third paragraph of the Methods): We selected hospitals for this study according to the following procedures. First, we extracted data from the Guangdong provincial STI CRS on the number of reported gonorrhoea cases of each city in Guangdong from 2014 to 2017. The cities with a higher rate of increase in the number of reported gonorrhoea cases between 2014 and 2017 than that of Guangdong province as a whole were selected for this study. Finally, within each city, the hospitals with a higher rate of increase in reported gonorrhoea cases between 2014 and 2017 than that of the city were then selected. A total of 10 cities (Shenzhen, Guangzhou, Foshan, Zhuhai, Zhongshan, Jiangmen, Dongguan, Huizhou, Jieyang, Meizhou) and 40 public hospitals were finally selected in the study. Trained interviewers contacted the hospitals and completed a questionnaire by transcribing all existing medical records with the assistance of staff members from Information section.

Comment 11: Page 6, line 15: What is the definition of the new gonorrhoea cases?

Response: We have rephrased "the new gonorrhoea cases" as "the newly diagnosed gonorrhoea cases" for clarity (see the fifth paragraph of the Methods). In China, all newly diagnosed STI cases in the health facilities are required to be reported to the STI case report system (CRS) (see the second and fifth paragraph of the Methods).

Comment 12: Page 6, line 22: how many years were included in this formula?

Response: We apologize for the confusion. We have clarified the number of years by rephrasing the description of the formula in the revised manuscript (see the fifth paragraph of the Methods). The average yearly rate of increase in incidence which was calculated as a geometric mean by the use of the formula: (incidence at years n divided by incidence at years m) $^{(1/[n-m])}$ -1.

Comment 13: Page 6, line 24: was a check of the distribution of the data performed to decide to use chi-square test?

Response: We thank the reviewer's reminder. We did not check the distribution of the data. We have rephrased the description of Statistical analysis to make it clearer for readers (see the eighth paragraph of the Methods).

Comment 14: There are several other measures included in the results section that have not been defined in the stats section. Please amend accordingly

Response: Thanks for the reviewer's suggestion. We have amended accordingly and provided definition for all the measures included in the Results (see the statistics analysis subsection under Methods). For example, we added the definitions for measures including gonorrhoea prevalence, reported incidence of gonorrhoea, and increased rate of screening amount for gonorrhoea.

Comment 15: Across all the results section, please report a statistical significance when presenting data from different years or from different methods.

Response: Thanks for the reviewer's suggestion. We have added the statistical significance for all data when assessing trend over years throughout the Results section (see the eighth paragraph of the Methods, and the Results section).

Comment 16: was a statistical method use to understand whether the male-to-female ratio decreased from 2014 to 2017.

Response: Thanks for the reviewer's suggestion. We have added a trend analysis for the male-to-female ratio data, which indicated that the decreasing trend was significant ($p < 0.001$) (see the first paragraph of the Results).

Comment 17: Page 6, lines 49-57: Please explain why in 2017 other cities were included.

Response: We apologize for the confusion. In 2014, only seven cities had a reported incidence of gonorrhoea over 10 cases per 100 000 in Guangdong Province. In 2017, the number of the cities increased from 7 to 13. Among those 13 cities, 8 cities were located in the Pearl River Delta region of Guangdong, 4 cities were in the Northern part of the province, and 1 city was in the Eastern part of the province. We have rephrased the description to explain why these other cities were included in 2017 (see the first paragraph of the Results section).

Comment 18: Page 7, line 10: is the 'average yearly' the annual increase in percentage?

Response: We apologize for the confusion. The 'average yearly' is the annual increase in percentage. We have used 'average yearly' instead of 'the annual increase' in the revised manuscript (see the second paragraph of the Results).

Comment 19: Page 7, line 15: please rephrase this, it is not clear to me the meaning. Do you mean that the smear test has been the most used in the past four years?

Response: We apologize for the confusion. We have rephrased the sentence as 'Overall, the smear test was the most frequently used among the five different testing methods between 2014 and 2017.' (see the second paragraph of the Results).

Comment 20: Page 8, lines 33-34: please define incidence rate.

Response: Thanks for the reviewer's reminder. We have provided the definition of incidence rate in the Methods section (see the statistical analysis subsection under Methods). The incidence rate was calculated by dividing the number of newly diagnosed cases by the total population of Guangdong province in a specified year.

Comment 21: Page 8, line 33-36: the results are not statistically significant for neither syphilis nor Chlamydia.

Response: Thanks for the reviewer's reminder. We have removed the results from the Results section (see the fifth paragraph of the Results).

Comment 22: Page 9, lines 35-42: please rephrase as it is not clear the concept you want to convey.

Response: Thanks for the reviewer's suggestion. We have rephrased the paragraph in the revised manuscript (see the first paragraph of the Discussion). A rapid increase in the number of reported gonorrhoea cases has been observed since 2014 in China. This study applied multiple sources of surveillance data from Guangdong province to identify the reasons. Our data suggest that expanded screening coverage, use of more sensitive diagnostics and increase in gonorrhoea prevalence are three potential contributors to the epidemic. Findings from this study provide insights for the design of tailored gonorrhoea intervention programs in China.

Comment 23: I am not sure if with the data presented you were able to discount from all the biases (more sensitive diagnostics and expanded coverage) there is still a "real" increase in gonorrhoea cases in the region of interest.

Response: We understand the reviewer's concern. As we showed in the second and third paragraph of the Results, and the third paragraph of the Discussion, the increased rate of gonorrhoea screening between 2014 and 2017 in the selected 40 hospitals was much lower than the increased rate of the number of reported gonorrhoea cases (figure 2). Additionally, data from the governmental sentinel

surveillance network indicated that the prevalence of gonorrhoea among males attending STI clinics has increased from 2.7% in 2015 to 3.6% in 2017. The proportion of males attending STI clinics engaging in risky sexual behavior has also grown rapidly since 2015. Therefore, we conclude that there was an increase in the population prevalence of gonorrhoea. We have revised the statement in a more careful way.

Comment 24: Page 9, lines 58-60: this is more a conclusion point rather than a discussion point.

Response: Thanks for the reviewer's suggestion. We have removed this point from the Discussion section to the Conclusions section (see the second paragraph of the Discussion and the Conclusions section).

Comment 25: Page 10, lines 14-16: please expand on the Zero Mark-up Drug policy and its efficacy and impact on the increase of gonorrhoea cases.

Response: Thanks for the reviewer's suggestion. We have provided more explanation on the Zero Mark-up Drug policy and related efficacy and impact on the increase of gonorrhoea cases in the revised manuscript (see the third paragraph of the Discussion).

Comment 26: Page 10, line 19-20: please include a reference for the work mentioned in brackets.

Response: Thanks for the reviewer's suggestion. We have added a reference for that work (see the third paragraph of the Discussion).

Comment 27: Page 10, line 24: The reference 29 included at the end of this paragraphs refers to a study done in Africa so I am not sure if this is relevant with the point expressed in the paragraph.

Response: Thanks for the reviewer's suggestion. We have cited another reference in China instead (see the third paragraph of the Discussion).

Comment 28: Page 10, lines 37-39: This statement is not clear to me. Are you suggesting that because of an increase in high risk sex behaviours there was an actual increase in the number of gonorrhoea cases? However the sentinel study didn't confirm this findings. In addition, I would suggest to add a multivariable analysis to take this into account, adjusting for the sex behavioural information.

Response: Thanks for the reviewer's suggestion. We have revised the statement in a more careful way. As we showed in the second and third paragraph of the Results, and the third paragraph of the Discussion, the increased rate of screening amount of gonorrhoea between 2014 and 2017 was much lower than the increased rate of the number of reported gonorrhoea cases accordingly (figure 2). Additionally, data from the governmental sentinel surveillance network indicated that the prevalence of gonorrhoea among male attending STIs clinic has increased from 2.7% in 2015 to 3.6% in 2017. The proportion of male attending STIs clinic engaging in risky sexual behavior has also grown rapidly since 2015. Therefore, we conclude there was an increase in the population prevalence of gonorrhoea.

We have added a multivariable analysis to examine the factors associated with gonorrhoea infection (see the sixth paragraph of the Results and Tables 3).

Comment 29: Page 10, line 46: please rephrase this concept. As far as I understood it is difficult to prove that the number of cases are underestimate or not and also please expand on why you think that this is not affecting the trend of incidence for gonorrhoea.

Response: We appreciate the reviewer's suggestion. We have rephrased this concept and removed the sentence 'although it would not change the trend of incidence of gonorrhoea' from the manuscript (see the fourth paragraph of the Discussion).

Comment 30: Page 1-18: the supplementary figures don't have titles and descriptions
Response: Thanks for the reviewer's reminder. We have added the titles and descriptions in the revised supplementary figures.

VERSION 2 – REVIEW

REVIEWER	Martina Furegato St' George's, University of London United Kingdom
REVIEW RETURNED	18-Sep-2019
GENERAL COMMENTS	I am happy with this revised version of the manuscript. Best wishes Martina