Author's response to reviews

Title: Prevalence of infectious keratitis in Central China

Authors:

Jin Cao (caojin20@163.com)
Yanning Yang (ophyyn@163.com)
Wanju Yang (mednature@163.com)
Ruoxi Wu (oph.roxy@gmail.com)
Xuan Xiao (xiao1111@163.com)
Jing Yuan (xyj711@163.com)
Yiqiao Xing (xing-yiqiao@yahoo.com)
Xiaodong Tan (350533383@qq.com)

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Author's response to reviews: see over
Dear Ms Erica Cruz:

Thank you very much for your letter and advice. We have revised the paper, and would like to re-submit it for your consideration. We have addressed the comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript. We hope that the revision is acceptable, and I look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Jin Cao

e-mail: cao520jin@163.com

We would like to express our sincere thanks to the reviewers for the constructive and
positive comments.

Response to reviewer 1: (Ioannis N. Petropoulos)

1) Introduction, page 3, lines 1-2, “Infectious keratitis...disability”. Not all references used are relevant and should also be less. The authors should consider including the paper by Bourne et al. Causes of vision loss worldwide, 1990-2010: a systematic analysis. Lancet Global Health 2013;1:e339-49

Response: Thanks for the reviewer’s kind suggestion. According to his/her advices, we have revised the manuscript which marked in red in the paper, page 4, Background section.

2) Introduction, page 4, lines 1-2, “China is estimates...globally”. In my opinion, the authors should provide a reference and a short explanation for their statement. There are specific reasons, besides infectious keratitis, on why China is expected to have largest number of people worldwide. Reasons such as economic growth, healthcare reform, improved safety standards, access to education, dietary changes will all likely result in an older/aging population and hence higher prevalence of diabetes, obesity, cataract, degenerative disorders (e.g. glaucoma, AMD). Of course it is important to know in what percentage infectious keratitis contributes to overall ophthalmic disease.

Response: Thanks for the reviewer’s suggestion. The manuscript has been modified, page 5, line 2 "Global Initiative For The Elimination Of Avoidable Blindness. Available at: http://www.who.int/inf-fs/en/fact230.html. 1999."

3) Methods, statistical analysis, page 8, line 7 “P < 0.05 indicated...”. Please explain whether you have adjusted the P value for the number of comparisons

Response: Yes, we have adjusted the P value, Pairwise comparison between multiple groups. After a row \(\times\) column for \(\times\) 2 have significant information to do further pairwise comparison, you can not reuse the original test level \(\alpha = 0.05\) as whether to reject \(H_0\) standards. Hypothesis testing is repeated several times, will allow expansion of the Type I error \(\alpha\), we must re-examine the provisions of the standard, according to a reject \(H_0\). When pairwise comparison between multiple groups, the level of the test is estimated by the following formula: \(\alpha' = \alpha / N\), where \(N = n(n-1)/2\) is the number of the desired test, \(n\) is the number of participating test group. We calculated according to the formula and adjusted the P value.

4) Did the authors apply any exclusion criteria? Measuring visual impairment (logMAR acuity as mentioned in the Methods) is a challenging task especially in rural or less educated populations

Response: Thanks for the reviewer’s suggestion. We have the definition and criteria of Blindness, low vision, and Corneal blindness (page 8). All members in the survey group were trained prior to the investigation, including standard procedure of the survey, visual examinations, diagnostic standard of corneal disease, and questionnaire filling. We will patiently explain to patients until they can successfully cooperate with the inspection.
5) A very good explanation is provided in the discussion about the high prevalence of pterygium lesions in those with corneal disease. Similarly, the comparison of study and WHO distributions regarding visual impairment is also relevant.

**Response:** Thanks for the reviewer’s kind suggestion. The analysis showed that increased age and low educational level were risk factors for infectious keratitis, whereas elder age, rural areas and the female gender, were high risk for infective corneal blindness. The age, gender, and education distributions of each cohort correspond to the population distributions of visual impairment reported by the WHO. (Page 12, line 9)

6) Punctuation and grammar mistakes are common across the text. Please Correct.

**Response:** We are ashamed for our unsatisfactory English and thank you very much for your cautious correction. We spent a lot of time, after we received your email, working through the paper and made some small changes marked in red in the paper to improve the English expression. Because the minor modifications are so many that we do not enumerate them.

**Response to reviewer 2:** (Maryam Ferdousi)

**Abstract:**

1) Methods section did not have enough detailed information about the recruitment of patients and the examinations

**Response:** Thanks for the reviewer’s kind suggestion. According to his/her advices, the manuscript has been modified, page 2, Methods section

2) Is the conclusion really reflecting the actual conclusion of the study?

**Response:** Thanks for the reviewer’s suggestion. The manuscript has been modified, page 3, conclusion section

**Introduction:**

3) There are referencing errors such as:

- "Infectious keratitis is still one of the main causes of ocular damage and visual disability" - none of the references cited for this phrase is an actual prevalence Study.

**Response:** Thanks for the reviewer’s kind suggestion. According to his/her advices, the manuscript has been modified" Infectious keratitis is still one of the main causes of corneal blindness and visual Disability"


- Based on the WHO, other main causes of visual impairment in 2002 are glaucoma (12.3%), age-related macular degeneration (AMD) (8.7%) and then
corneal opacities (5.1%)

Response: Thanks for the reviewer’s kind suggestion. The manuscript was revised, I have rewrite “Infectious keratitis is still one of the main causes of ocular damage and visual disability” to “Infectious keratitis is still one of the main causes of corneal blindness and visual disability”, Whitcher JP, Srinivasan M, Upadhyay MP. Corneal blindness: a global perspective. Bull World Health Organ. 2001;79:214–221.

4) There are phrases which need references such as:
o Through the perseverance of public health programs, the morbidity of corneal diseases due to Chlamydia trachomatis, Onchocerciasis, and leprosy have been controlled relatively stable.

o China is estimated to have the largest number of blind people globally

o Is the China’s First National Sample Survey of Disabled Persons really suggested infectious keratitis as a major cause of corneal blindness?
Response: Thanks for the reviewer’s kind suggestion. The text had already been marked up with corrections marked in red in the paper, page 5, line 11. I have rewrite “China’s First National Sample Survey of Disabled Persons suggested that infectious keratitis was a major cause of corneal blindness, accounting for approximately one-fourth of the cases of blindness in China.” to “China’s First National Sample Survey of Disabled Persons suggested that corneal disease as a major cause of blindness and low vision ranks second only to cataract in china, and the prevalence of corneal blindness and low vision was 11.5/10000, accounting for approximately one-sixth of the cases of blindness in China.”

5) Although some demographic characteristics of the patients are evaluated in this study, the risk factors of infectious keratitis were not evaluated in this study like it says in the objective
Response: Thanks for the reviewer’s kind suggestion. Table 4 “Univariate analysis of the prevalence of infectious corneal diseases” indicate that infectious keratitis presented in higher prevalence in the patients who live in rural areas and those receiving less education, and the prevalence increased with age. According to the reviewer’s advices, we discussed if the gender constitutes a risk factor, and devoted a lengthy and full discussion to this topic access to raw data, we believe that the gender is not the ultimate risk factors for Infectious keratitis in central China, and the proper interpretation and analysis of the result was carried out in the result and discuss section marked in red in the paper.

Methodology:
**Response:** We are sorry for such a translation error, “corneal doctors” means Doctors who specialize in corneal and external diseases. The “corneal doctors” has been modified to “specialized doctors”, page 7, line 7

**Response:** corneal disease is about 0.4%. The sample size is calculated using the formula: \( n = Z^2 p (1-p)/B^2 \). While \( p = 0.004 \), \( B = 0.1p \), \( Z_{0.05/2} = 1.96 \), the sample size is about 100000. The response rate is required to be more than 80%, in addition to the sample loss, the sample size is required to be at least 120000. According to the results from the Fifth National Population Census in 2000, there are a total population of 0.44 billion in the 10 provinces (municipalities or autonomous regions), and the sampling fraction is about 3/10000. The multi-stage stratified cluster random sampling method was employed in the present study. A city was randomly sampled from selected province, and then a district or county was randomly sampled from the city. Following the random sample of the sub-district offices or townships from districts or counties, the neighborhood communities or villages were then sampled randomly from the sub-district offices or townships. Following the method of the published literature, all sampled neighborhood communities or villages were divided into clusters, each containing about 1000 persons, in terms of registered populations and locations. All clusters were then numbered and sorted, and the simple random sampling method was adopted to sample the clusters.

**Response:** When the corneal stromal infiltration (whether there was epithelial defect or not), or corneal ulcer was more than 1 mm² (whether there was hypopyon or not), further corneal smears and cultures were performed for etiological examinations of infectious corneal ulcer. Cases with corneal opacity, scar, eyeball atrophy, anophthalmos, together with medical history or medical records that prove the sequelae are caused by bacterial, viral, fungal or Acanthamoeba keratitis, are diagnosed as infectious corneal disease. As to those without definite diagnosis, the final diagnosis is validated by specialists in the survey group according to the eye pictures and survey data.

**Results:**

**Response:** Thanks for the reviewer’s kind suggestion. It's a pity that our study is lack
of the prevalence of corneal blindness in both urban and rural area. However, the lack of investigation, as the reviewer said, is partially compensated by the statistical results that Infectious corneal diseases is the major Distribution of causes of corneal blindness (table 5). The demographic characteristics of the participants include age, gender, education and rural - urban disparities distributions of each cohort are detailed in table 4. Based on the survey results, we believe that the gender is not the ultimate risk factors in central China.

Conclusion:

- How educational distribution has been evaluated in this study and what is the definition of lower education levels?

  **Response:** lower education levels means education level less than high school degree.

- There should be no new material introduced in the conclusion. The association between the prevalence of the disease, gender and educational level needs to be introduced in the results section initially.

  **Response:** Thanks for the reviewer’s kind reminding. The manuscript has been modified, the material introducing were removed from discussion section to the conclusion section and marked in red in the paper.