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Reviewer A

I would like to comment the team for their stewardship programs at their hospital and their sustained efforts with improvement of antibiotic use through the COVID period.

Reply: We thank the reviewer for your time and the positive comments about our study. We have followed your suggestions and modified text to address the concerns. Detailed responses are as follows.

Comment 1: The authors very nicely showed decrease in APP and reduction in antibiotic consumption. They talked about financial incentives to influence antibiotic use. I was wondering if the authors could describe this in a little bit more detail. What was performed at their institution - e.g. what was the reward or what was the fine? What were the pushbacks or obstacles the team had to encounter to implement this?

Reply: Thank you very much for pointing out the lack of detailed description about financial incentives in our study. In the method-quality premium section (lines 153-160), we have described four measurements for normative antimicrobial management, however the article did not mention the specifically amount of rewards and fine. As the reviewer suggested, we issued a detailed reward and fine strategy as a supplemental table in the manuscript (Table S2). And we also described obstacles the team have encountered when once the implemented the quality premium in the discussion part. Changes were marked in red.

Changes in the text:

We added description in text: "The performance score would be deducted 0.5~2 points depending on the increase of antibiotic consumption compared with prior month. Conversely, the performance score would be increased 1 point according to the growth of prescription of unrestricted antimicrobials. The performance score was associated with bonus. Detailed measurements for quality premium of antimicrobial stewardship were shown in Table S2." We added a detailed reward and fine strategy as a supplemental table in the manuscript (lines 160-166): "The quality premium in

our study have been doubted to increase in dissatisfaction, lack of motivation especially on some clinical departments with higher infectious patient admission rate. In order to address the resistance and refusal, the MAMS programme strengthen communication with clinic and make prompt adjustments to the measurements of quality premium according to physicians' suggestions." (lines 310-316).

Comment 2: The authors have showed decrease in antibiotic use (in terms of DDD / proportion of patients on antibiotics). However, was there detail on safety aspects of the strategy? e.g. impact on re-infections / readmission during the corresponding period?

Reply: Thank you for your suggestion on improving the quality of our research. The safety aspects is also very important in MAMS programme and antibiotics should be used with proper regulation. The reduction of antibiotic use can reduce bacterial resistance and health care costs. However, it is also concerned that the effectiveness of anti-infection regimen is weakened. In our article, the decrease in antibiotic use (both in antibiotic consumption and antimicrobial prescription percentage) were not blind but following the Guiding Principle of Clinical Use of Antibiotics published by National Health and Family Planning Commission of China. In addition, pharmacist on examining antibiotic prescriptions has been performed during the whole study period and make sure of rational use of antibiotics. The relationship of re-infections, bacterial resistance and rational use of antibiotics still need further study based on the result of this article in the future.

Comment 3: For the audit and feedback system - who was in charge of the programme? Pharmacist or physicians?

Reply: Thank you for the detailed comment. In our hospital, five pharmacists majored in antibiotics with certificates issued by the Chinese Hospital Association were in charge of the audit and feedback system. Changes were marked in red.

Changes in the text: "Audit and feedback were used to confirm the proper use of antimicrobials. Pharmacists who majored in antibiotics with certificates issued by the Chinese Hospital Association were in charge of this programme." (lines 170-173)

Comment 4: The authors rightfully mentioned that this study may not reflect true

antibiotic trends across most hospitals during the COVID-19 period, given that they were not a designated infectious diseases facility. However, if we look at the supplied graphs or tables / there was a slight increase in antibiotic consumption during the COVID-19 period. Could the authors comment on this?

Reply: We appreciate your comment. The slight increase in antibiotic consumption during the COVID-19 period was occurred in January 2020 (Fig 2A), however, the ITS analysis of antibiotic consumption (Fig 5A) did not increase at the same observation point. This phenomenon demonstrated that the result of ITS analysis was unlikely to change even the abnormal fluctuations appeared in few observation points.

Reviewer B

The article is looking at the impact of the antimicrobial stewardship programme on antimicrobial use in a teaching hospital in Shanghai. The article is well structured. However, there are some major points to address:

1. INTERVENTION.

Comment 1: The stewardship programme consisted of 3 different parts. Did they all start at the same time? The educational part, how long was it? This part needs more information about when and how long each of the part stewardship programmes lasted.

Reply: Thank you very much for your time and your suggestion. The stewardship programme in our study consisted of 4 different parts: financial incentives, antibiotic restriction, audit and feedback, and education, all of the 4 parts were started at the same month (January 2019). The four parts of interventions were given throughout the whole intervention period (January 2019-December 2020) and were still conducted till now. We have added details in lines 118-119 with changes in red.

Changes in the text: "All of the interventions were performed on January 2019 and lasted the whole intervention period and still in progress till this article published." (lines 118-119).

2. OUTCOMES.

Comment 2: The authors looked at two outcomes: antibiotic consumption and the percentage of antibiotic prescription. Antibiotic consumption was described as DDD

per 100 patient per day. However, in the segmented regression analysis, the authors are talking about DDD per month. The outcome variable should be stated more clearly and be consistent. Did the authors consider looking as well at age-sex adjusted antibiotic consumption?

Reply: Thanks again for pointing out the inconsistent statements in our study. (1) Antibiotic consumption was defined as DDD per 100 patient per day, and "DDDs per 100 patient per day (DDDs/100 PD)" was the unit of antibiotic consumption. And we use monthly antibiotic consumption data for segmented regression analysis. We have changed the expressions of antibiotic consumption in segmented regression analysis part as suggested. (2) In our study, MAMS programme was carried out to the whole hospital and we would like to assess the effectiveness of this progrmme with priority. Age-sex adjusted antibiotic consumption deserves further investigation and we would like to take intensively study based on the existing results in the future. We have proofread our statement thoroughly and made changes in lines 274-277, Table 3, and Figure 5A with revisions marked in red.

Changes in the text: ITS analysis indicated an upward trend for monthly antibiotic consumption (0.12 DDDs/100 PD, P = 0.378) before MAMS intervention and a significant downward trend (-12.54 DDDs/100 PD, P < 0.001) after the first month of MAMS intervention (**Table 3, Figure 5A**). (lines 274-277)

3. STATISTICAL ANALYSIS.

Comment 3: In the result part, the authors presented results from before and after analysis; however, nothing about this is mentioned in the Statistical analysis part. To evaluate the impact of the stewardship program, the authors implemented segmented regression analysis for ITS.

Reply: We thank reviewer for the comment. In the result part, comparisons of the monthly values of the measures for antibiotic use from before and after the intervention were conducted using ANOVA or t-test. And we have mentioned the method of comparisons Statistical analysis section (lines 223-225).

Comment 4: It is recommended in the literature that to achieve robust estimates of change minimum of 100 cases per time is needed [1]. Did the authors achieve this?

Reply: We thank the reviewer for this comment. More time points are not always

better and too many observation points may not represent the current trend. Power increases with the number of time points, but it is not always preferable to have more data points where historical trends have changed substantially, as this would not provide an accurate depiction of the current underlying trends [2]. If a very long preintervention period is included, there is a risk that trends may have historically differed from current trends, which raises doubts about the validity of the comparison. The minimum number of data points is a decision driven by the statistical requirements for the analysis and will depend on the variability of the data and the type of statistical model used. For example, to model a seasonal effect, a minimum of 12 data points will be required [3]. In our study, the number of data points was fulfill the purpose of the research.

Comment 5: Did the authors assess the assumption that the observations are independent? If not, why?

Reply: Thank you very much for the comment. The assumption that the observations are independent is often violated in time series data and the reason is autocorrelation, a phenomenon which consecutive observations tend to be more similar to one another than those that are further apart. However, other variables will largely explain the autocorrelation in many epidemiological data and residual autocorrelation is rarely a problem after controlling these factors [3]. And in the existing work, there is very little evidence of autocorrelation and even less after adjustment for seasonality. We have evaluated the residual autocorrelation after establish regression model in our study and there is no sign of autocorrelation.

Changes in the text: We have carefully reevaluated the residual autocorrelation of our study. The result was added in statistical analysis part (lines 224-225) with red marks: "After controlling seasonality, residual autocorrelation was assessed by examining the plot of residuals and the partial autocorrelation function." (lines 224-225)

Comment 6: The estimation of the absolute change and the relative change would be easier and clearer for a reader, and interpretation of the results. As well, I would recommend presenting the post-intervention trend in segmented regression rather than the change in the trend after the intervention.

Reply: We sincerely thank reviewer for the meaningful suggestion. Segmented regression can provide valuable evidence for the effectiveness of population-level healthcare interventions. There are many different designs to evaluate the time series data requiring various methodological considerations among which the estimations of the absolute change and the relative change also are frequently used in some study. In our study, the presentation of ITS analysis followed the basic ITS design with a standard form to get better analysis of the changes in trend after the MAMS interventions.

4. RESULTS.

Comment 7: The figures for the segmented regression analysis should include the line representing the start of the intervention period. Would be interesting to see here as well what numbers would be if the intervention would never happen. From the Figure 5, it is visible that were was some change in level in December 2018 and December 2019. What did happen in December 2018 as there is a change? Was another programme implemented? If so, did the authors adjusted for that?

Reply: We sincerely thank the reviewer again for the kindly comment. In Figure 5, there are two visible changes in December 2018 (Change 1) and December 2019 (Change 2). The explanations are as follows: Change 1 shows downward trend in both antibiotic consumption and percentage of antibiotic prescriptions. The declining line connects two time point (December 2018 and January 2019). Antibiotic consumption and percentage of antibiotic prescriptions fall in January 2019 compared with December 2018, which potentially associated with instant efficacy of MAMS interventions (The MAMS programme initiated in January 2019). And the ITS analysis indicated the reduction in antibiotic consumption (coefficient = –12.537, $P <$ 0.001) and a downward trend in the percentage of antibiotic prescriptions (coefficient = –0.165, $P = 0.049$). Change 1 proved the notable influence of MAMS interventions. Change 2 is a declined line connecting December 2019 and January 2020 (the start of COVID 19 period). However, we didn't find any statistical significance by ITS analysis. It is demonstrated that we should combine Figure 5 with Table 3,4 to interpret results of ITS analysis.

Changes in the text: We redraw the figure of segmented regression analysis of our study. In Figure 5, a dotted line was added to show the start of the intervention period

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(January 2019).

Reference

1. Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Therapeut 2002; 27:299-309.

2. Lopez Bernal J, Soumerai S, Gasparrini A: A methodological framework for model selection in interrupted time series studies. Journal of clinical epidemiology 2018, 103:82-91.

3. Bernal JL, Cummins S, Gasparrini A: Interrupted time series regression for the evaluation of public health interventions: a tutorial. International journal of epidemiology 2017, 46(1):348-355.