Response to Reviewer A:

Comment 1: The title and aim indicates that the review is about CRP's ability to guide antibiotic prescription. However, the study is about CRP's ability to reduce antibiotics prescription. I think that "reduce" is the right word. Furthermore it should be stated "in adults" since the focus on adults is an important feature of the study. This is of course easy to change - but also important.

Reply 1: Thank you for your suggestion. According to your suggestion, the title of the manuscript has been rephrased into "C-reactive protein testing to reduce antibiotic prescribing for acute respiratory infections in adults: a systematic review and meta-analysis", and we have also made amendments to other expressions in the manuscript as appropriate (see Page 1, line 2-3).

Comment 2: ARI is to me an uncommon abbreviation. I am used to "acute RTI".

Reply 2: Thank you very much for your suggestion, I have retrieved articles related to acute respiratory infections and found that the abbreviation of "ARI" is more commonly used in most articles compared with "acute RTI"(1-4), and we think that the abbreviation of "ARI" is more suitable for our manuscript, so we use the "ARI" in our manuscript.

References are as follows:

[1]Aabenhus R, Jens lrik S Jensen, JØRgensen K J, et al. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. Cochrane Database Syst Rev 2014;11(10):CD010130.

[2]Jolliffe DA, Griffiths CJ, Martineau AR. Vitamin D in the prevention of acute respiratory infection: systematic review of clinical studies. Steroid Biochem Mol Biol 2013;136:321-9.

[3]Zhang Y, Muscatello DJ, Wang Q, Yang P,et al. Hospitalizations for Influenza-Associated Severe Acute Respiratory Infection, Beijing, China, 2014-2016. Emerg Infect Dis 2018;24(11):2098-2102.

[4]Colley JR, Miller DL. Acute respiratory infections. Chest 1989;96(3 Suppl):355S-360S.

Comment 3: I do not understand what is meant by "CRP dose on enrolment" line 77 and 135.

Reply 3: Thank you again, we are sorry for the inaccurate use of "CRP dose on enrolment". We have modified "CRP dose on enrolment" to "CRP level as the recommended threshold of antibiotic prescribing" (see Page4, line 88; Page6, line148,151).

Response to Reviewer B:

Comment 1: Could you elaborate further on the type of upper (you pointed two groups of upper ARIs in the text) and lower ARIs (which ones, e.g. acute bronchitis, pneumonia, acute exacerbation of COPD, and so on) were included in the reviewed studies?

Reply 1: Thank you very much for your suggestion. According to your suggestion, we have elaborated further on the type of upper and lower ARI as follows: Patients in three studies were low ARI, included only acute exacerbation of chronic obstructive pulmonary disease (AECOPD), while in four studies were upper ARI, included rhinosinusitis, rhinitis, pharyngitis and acute cough. (see Page5, line114-116). You have mentioned that two groups of upper ARI were pointed in our text. We apologize for our inaccurate presentation. We wanted to express the two groups are CRP testing group and routine care group in the manuscript, the inappropriate expression has been revised.

Comment 2: Please decipher the abbreviations inside the text and under table 1 (e.g. T, C). What do you mean under “CRP dose” (CRP level as the recommended threshold of antibiotic)?

Reply 2: Thank you very much for your suggestion. we have modified the "T, C" to "CRP testing, Routine care" (see Page19). We have modified the "CRP dose" to "CRP level as the recommended threshold of antibiotic prescribing" (see Page4, line 88; Page6, line148,151).

Comment 3: Some English correction is needed.

Reply 3: Thank you a lot for your reminder. We are so sorry for the inaccurate and improper content in manuscript. We have modified the inaccurate content in manuscript and marked in red. Some major revisions are listed as follows.

3.1 We made the subgroup analyses of antibiotic prescribing rate at the index consultation. The subgroup analyses was conduced by different type of ARI and different CRP level as

recommended of antibiotic prescribing. It is showed that CRP testing significantly reduce the antibiotic prescribing rate compared with the routine care in low ARI [RR=0.71, 95%CI (0.65,0.78), P<0.00001], but not in upper ARI [RR=0.83, 95%CI (0.66, 1.03), P =0.09]. Subgroup analyses by different CRP level as recommended threshold showed that using of 40mg/L as the recommended threshold was the most obvious to reduce the antibiotic prescribing compared with the routine care. However, there were not significantly different between CRP testing and routine care using 50mg/L as the recommended (AppendixⅢ).(Page6, line147-154).

3.2 CRP testing can reduce the antibiotic prescribing in adult patients with ARI, which is safe and will not affect clinical recovery. However, the CRP level as the recommended threshold of antibiotic prescribing is not consistent. Considering the individual difference of patients, physicians should make clinical decisions combined with patient's preferences, best available evidence and experience of professionals. (Page9, line229—Page10, line 232).

Comment 4: In the COVID-19 era, CRP testing is being used not as a guide to antibiotic prescribing, but as an inflammatory marker. Could you elaborate on it a little bit more in the discussion section?

Reply 4: Thanks a lot for your suggestion. We have added the content about CRP and COVID-19 as follows: COVID-19 is the highly pathogenic SARS coronavirus pneumonia that infects human. Inflammatory reaction plays a critical role in COVID-19. Inflammatory storm can increase the severity of COVID-19 and lead to serious complications and death (1-3). CRP is a biomarker of inflammatory response, which can predict the severity and prognosis of COVID-19(4-5). A retrospective study conducted in China found that patients with CRP level> 41.8 mg/L in COVID-19 were more likely to develop severe disease(6). A study of COVID-19 patients who need mechanical ventilation shows that CRP level can be used to guide escalation of treatment in patients with COVID-19–related hyperinflammatory syndrome(7). However, the pathogen of infection in COVID-19 is coronavirus, and antibiotics are aimed at bacterial infection, so CRP testing cannot be used as a guide to antibiotic prescribing for patients with COVID-19.For patients with overactivated inflammatory response in COVID-19, the recent research recommended glucocorticoid for

anti-inflammatory treatment (8-9).(see Page8; line196—Page9; line 207).

References are as follows:

［1］Yang P, Ding Y, Xu Z, et al. Epidemiological and clinical features of COVID-19 patients with and without pneumonia in Beijing, China. medRxiv 2020; 2020-2022.

[2] Zumla A, Hui D S, Azhar E I, et al. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. Lancet 2020; 395(10224):e35-e36.

[3] Wan S, Yi Q, Fan S, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). medRxiv 2020; 2020-2022.

[4] Zhang T, Huang W S, Guan W, et al. Risk factors and predictors associated with the severity of COVID-19 in China: a systematic review, meta-analysis, and meta-regression. J Thorac Dis 2020;12(12):7429-7441.

[5] Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020; 63(3):364-374.

[6] Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol 2020; 127:104370.

[7] Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol 2020; 146(1):128-136.

[8] Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med 2020;383(25):2451-2460.

[9] WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA 2020;324(13):1330-1341.