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Guidelines

Recommendations for antibacterial therapy in adults with COVID-19 – an evidence based guideline

Elske Sieswerda [1,*], Mark G.J. de Boer [2], Marc M.J. Bonten [3], Wim G. Boersma [4], René E. Jonkers [5], Roel M. Aleva [6], Bart-Jan Kullberg [7], Jeroen A. Schouten [8], Ewoudt M.W. van de Garde [9,10], Theo J. Verheij [11], Menno M. van der Eerden [12], Jan M. Prins [13], W. Joost Wiersinga [13,**]

[1] Department of Medical Microbiology and Infection Control, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
[2] Department of Infectious Diseases, Leiden University Medical Center, Leiden, the Netherlands
[3] Department of Medical Microbiology, University Medical Centre Utrecht, Utrecht, the Netherlands
[4] Department of Pulmonary Diseases, Northwest Hospital Group, Alkmaar, the Netherlands
[5] Department of Respiratory Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
[6] Department of Pulmonary Diseases, Máxima Medisch Centrum, Eindhoven, the Netherlands
[7] Radboud Center for Infectious Diseases and Department of Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands
[8] Department of Intensive Care, Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, the Netherlands
[9] Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, the Netherlands
[10] Division of Pharmacoepidemiology and Clinical Pharmacology, Department of Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands
[11] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
[12] Department of Pulmonary Diseases, Erasmus MC, Rotterdam, the Netherlands
[13] Department of Internal Medicine, Division of Infectious Diseases, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

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ABSTRACT

Scope: The Dutch Working Party on Antibiotic Policy constituted a multidisciplinary expert committee to provide evidence-based recommendation for the use of antibacterial therapy in hospitalized adults with a respiratory infection and suspected or proven 2019 Coronavirus disease (COVID-19).
Methods: We performed a literature search to answer four key questions. The committee graded the evidence and developed recommendations by using Grading of Recommendations Assessment, Development, and Evaluation methodology.
Questions addressed by the guideline and Recommendations: We assessed evidence on the risk of bacterial infections in hospitalized COVID-19 patients, the associated bacterial pathogens, how to diagnose bacterial infections and how to treat bacterial infections. Bacterial co-infection upon admission was reported in 3.5% of COVID-19 patients, while bacterial secondary infections during hospitalization occurred up to 15%. No or very low quality evidence was found to answer the other key clinical questions. Although the evidence base on bacterial infections in COVID-19 is currently limited, available evidence supports restrictive antibiotic use from an antibiotic stewardship perspective, especially upon admission. To support restrictive antibiotic use, maximum efforts should be undertaken to obtain sputum and blood culture samples as well as pneumococcal urinary antigen testing. We suggest to stop antibiotics in patients who started antibiotic treatment upon admission when representative cultures as well as urinary antigen tests show no signs of involvement of bacterial pathogens after 48 hours. For patients with secondary bacterial respiratory infection we recommend to follow other guideline recommendations on antibacterial treatment for patients with hospital-acquired and ventilator-associated pneumonia. An antibiotic treatment duration of five days in patients with COVID-19 and suspected bacterial respiratory infection is recommended upon improvement of signs, symptoms and inflammatory markers. Larger, prospective studies about the epidemiology of bacterial infections in COVID-19 are urgently needed to

* Corresponding author: Elske Sieswerda, Department of Medical Microbiology and Infection Control, Amsterdam UMC, Amsterdam, the Netherlands. Tel.: +31 6 25716442; fax: +31 20 4440473.
** Corresponding author: W. Joost Wiersinga, Department of Internal Medicine, Division of Infectious Diseases, Amsterdam UMC, Amsterdam, the Netherlands.
E-mail addresses: e.sieswerda@amsterdamumc.nl (E. Sieswerda), w.j.wiersinga@amsterdamumc.nl (W.J. Wiersinga).

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confirm our conclusions and ultimately prevent unnecessary antibiotic use during the COVID-19 pandemic. **Elske Sieswerda, Clin Microbiol Infect 2021;27:61**

Scope

The 2019 Coronavirus (COVID-19) pandemic due to the novel SARS Coronavirus (SARS-CoV-2) has resulted in a sudden, large and prolonged increase in hospitalizations of patients fulfilling the criteria for community-acquired pneumonia (CAP). SARS-CoV-2 can lead to a wide spectrum of disease, ranging from very mild symptoms of upper respiratory tract infection to life-threatening pneumonia. Severe disease is frequently associated with high inflammation marker levels. It is therefore challenging to define if a patient fulfilling criteria for CAP who is positive for SARS-CoV-2 has a bacterial co-infection upon admission. During hospitalization it may be difficult to distinguish between severe COVID-19 and bacterial secondary infections.

In several reports the majority of hospitalized patients with COVID-19 were treated with broad-spectrum antibiotics with unknown efficacy [1–11]. As COVID-19 patients frequently need prolonged hospitalization and respiratory support, unnecessary antibiotics upon hospitalization may increase the individual risk of subsequent hospital-acquired pneumonia (HAP) caused by resistant bacteria and other adverse events [12,13]. On a population level, universal antibiotic prescriptions for all or the vast majority of hospitalized COVID-19 patients can lead to a steep increase in antibiotic use during a pandemic and as a result, a potential increase in antimicrobial resistance rates [14].

The Dutch Working Party on Antibiotic Policy (SWAB) coordinates activities in the Netherlands with the aim to optimize antibiotic use, to contain the development of antimicrobial resistance, and to limit the costs of antibiotic use. In 2017 a joined guideline on the management of hospitalized patients with CAP was issued [15,16]. Now, our goal was to provide evidence-based recommendations about the empirical antibacterial treatment of hospitalized adults ($\geq$18 years old) with a respiratory infection and suspected or proven COVID-19.

Methods

We constituted a committee of experts of several disciplines, including experts in guideline development and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. We aimed to answer four key questions relevant for the clinical setting (Table 1). A high likelihood of COVID-19 was defined as an illness most likely COVID-19 as concluded by the treating clinician based on signs, symptoms, background prevalence of SARS-CoV-2, an epidemiological link, results of laboratory tests, imaging and other diagnostic tests, while awaiting the confirmatory SARS-CoV-2 test. Proven COVID-19 was defined as an illness most likely COVID-19 as concluded by the treating clinician and confirmed with a SARS-CoV-2 test.

A systemic literature review was performed by one author (ES) on 5 May 2020 in PubMed and LitCovid and references from relevant articles. The search strategy was: ((coronavirus and 2020) or COVID-19 or SARS-CoV-2) and (bacteria* or antibiotic* or antibacterial). Two authors (JMP, WJW) checked the original literature search. The panel anticipated on limited high quality evidence due to the recent emergence of SARS-CoV-2 and reports on adults were therefore included irrespective of the study design and outcomes studied. We defined co-infections as (suspected) bacterial pneumonia in addition to COVID-19 in patients within 48 to 72 hours of admission for (suspected) COVID-19. Secondary infections were defined as (suspected) bacterial pneumonia beyond 48 to 72 hours of hospitalization for COVID-19. We did not include evidence on the diagnosis of COVID-19, the antiviral treatment of SARS-CoV-2 nor on the antifungal treatment of patients with a suspicion of COVID-19 Associated Pulmonary Aspergillosis. Case-reports and case-series with less than ten patients were not included.

For each key question we developed short evidence summaries, which were subsequently assessed using the GRADE system by two authors (ES, WJW) [17]. Quality of evidence for clinically relevant outcomes was graded from high to very low. During video conferences, available literature and quality of evidence was presented. After discussion, the committee formulated draft recommendations as strong or weak based on the GRADE system. When evidence could not be obtained, recommendations were provided based on opinions, clinical experiences and consensus (good practice statements, GPS). During a final video-conference, recommendations were approved by the committee. Based on a subsequent peer-review process with members of relevant professional medical societies, the definitive guidelines were drawn up and approved by the board of SWAB. The full guidelines text, literature review and rebuttal of the received commentaries are available in the supplementary material.

During the submission process of the current manuscript, a relevant systematic review and meta-analysis on bacterial infections in COVID-19 was published [18]. We additionally assessed this systematic review and incorporated it in the current manuscript. Grading of evidence and recommendations were unchanged.

Questions adressed by the guidelines and recommendations

A summary of all recommendations including final grading of evidence is provided in Table 2. Our GRADE table is presented in Supplementary table 1.

1. *What is the risk of bacterial pneumonia in patients with proven or high likelihood of COVID-19?*

Supplementary table 2 provides an evidence summary of studies reporting on bacterial infections in patients with proven or

Table 1
Key questions

1. What is the risk of bacterial pneumonia in patients with proven or high likelihood of COVID-19?
2. What are the causative bacterial species in patients with proven or high likelihood of COVID-19 and bacterial pneumonia?
3. What is the optimal approach in diagnosing or refuting bacterial pneumonia in patients with proven or high likelihood of COVID-19?
4. What is the optimal empirical antibiotic choice for patients with proven or high likelihood of COVID-19 and suspected bacterial pneumonia?

Table 2
Summary of recommendations

Recommendation	Strength	Quality of evidence
1. We generally suggest restrictive use of antibacterial drugs in patients with proven or a high likelihood of COVID-19. This especially applies for patients upon admission who are mild to moderately ill	Weak	Very low
2. We suggest that exceptions for the restrictive use of antibacterial drugs can be made for patients with proven or a high likelihood of COVID-19 who present with radiological findings and/or inflammatory markers compatible with bacterial co-infection. Other exceptions are patients who are severely ill or immunocompromised*	Weak	GPS
3. We recommend maximum efforts to obtain sputum and blood for culture as well as pneumococcal urinary antigen testing before start of empirical antibiotic therapy in patients with proven or high likelihood of COVID-19 upon admission	Strong	GPS
4. In case of suspected bacterial co-infection, we suggest against empirical antibiotic treatment covering atypical pathogens in patients with proven or high likelihood of COVID-19 hospitalized at the general ward. *Legionella* urinary antigen testing should be performed according to local and/or national guidelines for CAP	Weak	Very low
5. We recommend that the empirical antibiotic regimens in case of suspected bacterial co-infection depends on the severity of disease and according to local and/or national guidelines. For those fulfilling criteria of mild and moderate-severe CAP, we recommend to follow local and/or national guideline recommendations on antibacterial treatment in CAP	Weak	Very low
6. We recommend to follow local and/or national guideline recommendations on antibacterial treatment for patients with COVID-19 and suspected bacterial secondary infection	Strong	GPS
7. We suggest to stop antibiotics when representative sputum and blood culture as well as urinary antigen tests taken before start of empirical antibiotic therapy in patients with proven or high likelihood of COVID-19 show no bacterial pathogens after 48 hours of incubation	Weak	GPS
8. We suggest an antibiotic treatment duration of five days in patients with COVID-19 and suspected bacterial infection upon improvement of signs, symptoms and inflammatory markers	Weak	GPS

* immunocompromised is defined as the use of chemotherapy for cancer, bone marrow or organ transplantation, immune deficiencies, poorly controlled HIV or AIDS, or prolonged use of corticosteroids or other immunosuppressive medications; GPS: good practice statement.

high likelihood of COVID-19. A study from China reported signs of bacterial co-infection upon hospital admission in 1 of 99 patients [19]. Another study from China reported no bacterial co-infections in 201 hospitalized patients with COVID-19, of whom 74% had sputum culture results available [20]. One study from the US reported no atypical pathogens in 115 patients with community-acquired COVID-19 [21]. Three single-centre Dutch cohort studies reported on bacterial co-infections in 107, 100 and 29 COVID-19 patients [22–24]. In these three cohorts, the percentage of patients with a potential bacterial respiratory co-infection upon admission was 8% or less and lower in patients presenting at the emergency department (less than 3%) compared to the two hospitalized COVID-19 populations (7-8%). We found no studies reporting prevalences of bacterial co-infections in patients in whom the diagnosis of COVID-19 was not yet confirmed.

Two studies from Wuhan in China reported on secondary infections in hospitalized COVID-19 patients [2,25]. One prospective cohort study of 41 confirmed COVID-19 patients reported 10% incidence of nosocomial, microbiologically-confirmed bacterial pneumonia or bacteraemia [25]. The authors did not separate data for pneumonia from bacteraemia. A larger retrospective multicentre study reported secondary infections (HAP; or bacteraemia) and ventilator-associated pneumonia (VAP) in 191 COVID-19 patients who had been discharged or had died at the end of the study [2]. The authors reported an overall incidence of 15% secondary bacterial infections. This number was lower in those who survived (<1%) compared to non-survivors (50%). In the overall cohort, 5% developed VAP during hospitalization. In contrast, VAP was diagnosed in up to 31% of those who received mechanical ventilation. A small cohort study of ICU-admitted COVID-19 patients in the US reported not a single bacterial co-infection found in respiratory and blood cultures during first 14 days of hospitalization [26].

A systematic review on bacterial and fungal co-infections in coronaviruses similarly reported an overall percentage of 8% co-infections in COVID-19 patients at any time during hospitalization [11]. The authors did not make a distinction between co-infections upon admission and secondary infections that occurred during hospitalization. Many of the reported infections were bacteraemia, suggesting the presence of bacterial infections other than pneumonia.

A systematic review and meta-analysis on bacterial infections in COVID-19 patients reported an overall proportion of bacterial infections of 7.1% (95% confidence interval [CI]: 4.6 − 9.6%) in 28 eligible studies [18]. The authors additionally assessed proportion of bacterial co-infections upon presentation, which was found in 3.5% (95% CI: 0.6 − 6.1%) of patients; and proportion of bacterial secondary infections after initial presentation, which was 15.5% (95% CI: 10.9 − 20.1).

2. *What are the causative bacterial species in patients with proven or high likelihood of COVID-19 and bacterial pneumonia?*

Reported bacterial pathogens in available studies of patients with COVID-19 are shown in Supplementary table 2. In eight studies information on bacterial pathogens was reported [19–26]. Three studies reported no bacterial pathogens [20,21,26]. The pathogens reported in COVID-19 patients with possible bacterial co-infection were mainly *Staphylococcus aureus*, *Haemophilus influenzae* and *Streptococcus pneumoniae*. Only three gram-negative bacterial species were reported in two patients. In one patient in China, both *Klebsiella pneumoniae* and *Acinetobacter baumannii* were isolated from respiratory material [19]. In one patient in the Netherlands, *Pseudomonas aeruginosa* was cultured from blood, but it was not described whether the bacteraemia was related to a suspected respiratory or other infection [24]. One positive PCR for *Mycoplasma pneumoniae* and no positive *Legionella* tests were reported [23]. The clinical severity of pneumonia was not reported in the available studies. As a consequence, it is unknown whether the cultured *S. aureus* in respiratory material was associated with severe pneumonia, as can be seen after an influenza virus infection, or with colonization of the respiratory tract.

Among two studies on secondary infections, one reported on bacterial pathogens [2,25]. In this small study from China, three gram-negative species were reported: 2/29 (7%) *Enterobacter cloacae* and 1/29 (3%) *A. baumannii* [10].

The systematic review and meta-analysis of Langford et al. reported identified bacteria in 188 studies on bacterial infections in COVID-19 patients [18]. *Mycoplasma* species were identified in n = 12, Enterobacterales spp in n = 11, *H. influenzae* in n = 8, *P. aeruginosa* in n = 5, *S. aureus* in n = 2, *A. baumannii* in n = 2 and

Enterococcus faecium in n = 1. Here no distinction was made between bacterial co-infection upon presentation and secondary infection after initial presentation. For 26 of 41 reported bacteria the source of identification was respiratory material, in the remainder this was unspecified.

3. *What is the optimal approach in diagnosing or refuting bacterial pneumonia in patients with proven or high likelihood of COVID-19?*

We found one meta-analysis summarizing 18 studies on prediction models for the diagnosis of COVID-19 [27]. Within five general prediction models, most common predictors were clinical or demographical factors, such as age, fever and other signs and symptoms. The other 13 studies assessed CT scan-based prediction models for the diagnosis of COVID-19. All studies were at high risk of bias and almost all were not externally validated. The studies did not report on alternative diagnoses such as bacterial pneumonia or co-infections. We found no other studies on diagnosing or refuting bacterial pneumonia in patients with COVID-19.

4. *What is the optimal empirical antibiotic choice for patients with proven or high likelihood of COVID-19 and suspected bacterial pneumonia?*

There were no studies yet evaluating the effectiveness and safety of specific antibiotic regimens in patients with proven or high likelihood of COVID-19 and suspected bacterial pneumonia.

Discussion

Based on current limited evidence, the vast majority of patients with proven COVID-19 respiratory illness presenting at the hospital does not have or develop a bacterial co-infection. Reported percentages of potential respiratory bacterial co-infections upon admission was 3.5% in cohort studies reporting on cultured bacterial co-infections, but the quality of evidence and therefore the accuracy of these percentages is very low. Based on the currently available evidence and antibiotic stewardship principles, the committee recommends restrictive use of antibacterial drugs in patients with community-acquired respiratory infection and proven or high likelihood of COVID-19. This especially applies to patients with mild or moderately-severe respiratory disease based on clinical assessment [16,28–30].

Several studies did not report details on the total number of patients from whom culture samples were obtained. In patients with a positive bacterial culture or PCR result from respiratory material, it was not reported how this result related to a clinically or otherwise confirmed diagnosis of bacterial co-infection. A substantial proportion of patients was already treated with antibiotics before hospitalization, decreasing the yield of bacterial cultures. Importantly, there were only data available for patients with (subsequently) proven COVID-19.

The committee agreed that clinicians should always assess the risk of a bacterial co-infection in patients with suspected COVID-19. However, in daily practice, it is difficult to distinguish viral from bacterial pneumonia [16,31]. Of note, the Infectious Disease Society of America (IDSA) guideline on CAP concluded that procalcitonin cannot be used in the decision to start or withhold antibiotics in patients with CAP [31]. The IDSA guideline on HAP and VAP performed extensive evidence summaries evaluating the additional value of using procalcitonin, CRP, or the Modified Clinical Pulmonary Infection Score plus clinical criteria for the diagnosis of HAP or VAP [12]. None of these diagnostic modalities were of additional value compared to clinical criteria alone. In current clinical practice, some hospitals do make use of procalcitonin to direct the initiation of antibiotic therapy in patients with suspected or proven COVID-19. This might be a valid strategy, however the evidence base for such a strategy is currently lacking. In daily practice, a combination of the clinical course of disease and results obtained from laboratory tests and imaging are leading in the assessment of the likelihood of bacterial co-infection in patients with COVID-19.

Therefore, as a good practice statement, the committee suggests that antibiotic therapy should be considered if the clinician has a high suspicion of bacterial co-infection in a patient with radiological findings and/or inflammatory markers compatible with bacterial co-infection. Other patients with proven or high likelihood of COVID-19 in whom it is reasonable to start empirical antibiotic therapy while awaiting diagnostic test results include those who are severely immunocompromised. These patients have a higher likelihood of deteriorating rapidly in the event of an untreated bacterial co-infection. We defined immunocompromised as use of chemotherapy for cancer, bone marrow or organ transplantation, immune deficiencies, poorly controlled HIV or AIDS, or prolonged use of corticosteroids or other immunosuppressive medications. In addition, the guideline committee endorsed the recommendation of the 2020 Surviving Sepsis Campaign guideline on COVID-19 to treat critically ill patients admitted to the ICU for COVID-19 with empiric antibiotic therapy while awaiting test results [32].

As the evidence base for our recommendations is limited, we recommend maximum efforts of to obtain sputum and blood cultures before start of empirical therapy in patients fulfilling criteria of CAP and proven or high likelihood of COVID-19 to support or refute the diagnosis of bacterial infection. An urinary pneumococcal antigen testing is recommended in all patients, as for COVID-19 patients we recommend to withhold antibiotic therapy in the group who do fulfil the formal criteria of mildly or moderately severe CAP [16,28–30]. A positive urinary pneumococcal antigen testing might support the diagnosis of bacterial co-infection, and thus lead to empiric antibiotic therapy.

The reported bacterial pathogens in patients with a co-infection seemed similar to those in regular bacterial CAP [16,31]. As there is no evidence for a specific superior empirical treatment strategy in patients with COVID-19 and bacterial pneumonia, we recommend to follow local and/or national guidelines for the antibacterial treatment of CAP [16,31,33]. As an example, in the Dutch SWAB guideline on CAP, preferred regimens depend on the severity of disease: for mildly and moderately severe CAP amoxicillin is recommended, for patients with severe CAP at the general ward a second or third generation cephalosporin is recommended [16]. Pneumonia due to atypical pathogens as a co-infection to COVID-19 are rarely reported in the literature. As a result, the committee suggests that routine empirical treatment of atypical pathogens such as *Legionella* and *Mycoplasma* spp. is not started in patients with proven or high likelihood of COVID-19 hospitalized. Again, it is recommended to perform *Legionella* urinary antigen testing according to the criteria mentioned in local and/or national guidelines [16,31,33].

The available evidence suggests a risk of up to 20% secondary infections in COVID-19 patients, especially in severely ill patients. There is no available evidence on the additional risk of such secondary infections in COVID-19 patients compared to other severely ill patients, and neither on causative pathogens. The committee thought it currently reasonable to assume that the risk of secondary infections in COVID-19 patients as well as the causative pathogens are similar secondary infections in hospitalized patients without COVID-19. It is currently unknown what the effect of antibacterial strategies is on outcomes of secondary infections in COVID-19 patients, including selective decontamination of the digestive tract. We therefore recommend to start empirical treatment, after obtaining cultures, in COVID-19 patients with suspected secondary

bacterial respiratory infection in accordance with local and/or national guideline recommendations on antibacterial treatment for patients with HAP and VAP. For patients without recent surveillance culture results, the antibacterial spectrum is suggested to include *S. aureus*, Enterobacterales, *P. aeruginosa*, *A. baumannii* and *H. influenzae, depending on local prevalences*.

The committee emphasizes the need for appropriate de-escalation in COVID-19 patients, in order to reduce unnecessary antibiotic use as much as possible [34,35]. As a good practice statement, we therefore suggest that, if antibiotics have been started, to stop those when representative sputum and blood culture and urinary antigen tests obtained before start of empirical therapy in patients with proven or high likelihood of COVID-19 show no pathogens after 48 hours of incubation. The guideline committee suggests that an antibiotic treatment duration of five days is likely sufficient in patients with COVID-19 and suspected bacterial co-infection upon improvement of signs, symptoms and inflammatory markers [16,31]. Procalcitonin levels could be used to support shortening the duration of antibacterial therapy in patients with sepsis if the optimal duration of antibiotic therapy is unclear [31,36].

In conclusion, this is an executive summary of a multidisciplinary guideline with recommendations for the empirical antibacterial treatment of hospitalized adults with a respiratory infection and proven or high likelihood of COVID-19. Such recommendations on treatment in COVID-19 patients need to be updated regularly, as the evidence on bacterial co-infections, secondary infections and the optimal management of COVID-19 patients expands. Although the evidence base on bacterial infections in COVID-19 is currently limited, available studies support restrictive antibiotic use from an antibiotic stewardship perspective upon admission. Larger, prospective studies on the epidemiology of bacterial co-infections and secondary infections in COVID-19, adjusted for antibiotic use and other confounders, are warranted to confirm our conclusions and ultimately prevent unnecessary antibiotic use during the COVID-19 pandemic.

Transparency declaration

Members of the preparatory committee reported the following potential conflicts of interest: ES: none; MGJDB: none; MJB: none; WGB: none; REJ: none; RMA: none; BJK: reports personal fees from Pfizer, outside the submitted work; JAS: none; EMWG: none; TJV: none; MMVE: none; JMP: none; WJW: reports support by the Netherlands Organization of Scientific Research (VIDI grant). No conflict of interest to disclose.

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Author contributions

Conception of the work: ES, MGJDB, JAS, JMP, WJW.

Data collection: ES, JMP, WJW.

Data analysis and interpretation: ES, MGJDB, MJB, WGB, REJ, RMA, BJK, JAS, EMWG, TJV, MMVE, JMP, WJW.

Drafting of the article: ES, MGJDB, JAS, JMP, WJW.

Critical revision of the article: MJB, WGB, REJ, RMA, BJK, EMWG, TJV, MMVE.

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Appendix A. Supplementary data

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