Efficacy and safety of azithromycin versus placebo to treat lower respiratory tract infections associated with low procalcitonin: a randomised, placebo-controlled, double-blind, non-inferiority trial

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Summary

Background Lower respiratory tract infections are frequently treated with antibiotics, despite a viral cause in many cases. It remains unknown whether low procalcitonin concentrations can identify patients with lower respiratory tract infection who are unlikely to benefit from antibiotics. We aimed to compare the efficacy and safety of azithromycin versus placebo to treat lower respiratory tract infections in patients with low procalcitonin.

Methods We conducted a randomised, placebo-controlled, double-blind, non-inferiority trial at five health centres in the USA. Adults aged 18 years or older with clinically suspected non-pneumonia lower respiratory tract infection and symptom duration from 24 h to 28 days were eligible for enrolment. Participants with a procalcitonin concentration of 0·25 ng/mL or less were randomly assigned (1:1), in blocks of four with stratification by site, to receive over-encapsulated oral azithromycin 250 mg or matching placebo (two capsules on day 1 followed by one capsule daily for 4 days). Participants, non-study clinical providers, investigators, and study coordinators were masked to treatment allocation. The primary outcome was efficacy of azithromycin versus placebo in terms of clinical improvement at day 5 in the intention-to-treat population. The non-inferiority margin was –12·5%. Solicited adverse events (abdominal pain, vomiting, diarrhoea, allergic reaction, or yeast infections) were recorded as a secondary outcome. This trial is registered with ClinicalTrials.gov, NCT03341273.

Findings Between Dec 8, 2017, and March 9, 2020, 691 patients were assessed for eligibility and 499 were enrolled and randomly assigned to receive azithromycin (n=249) or placebo (n=250). Clinical improvement at day 5 was observed in 148 (63%, 95% CI 54 to 71) of 238 participants with full data in the placebo group and 155 (69%, 61 to 77) of 227 participants with full data in the azithromycin group in the intention-to-treat analysis (between-group difference –6%, 95% CI –15 to 2). The 95% CI for the difference did not meet the non-inferiority margin. Solicited adverse events and the severity of solicited adverse events were not significantly different between groups at day 5, except for increased abdominal pain associated with azithromycin (47 [23%, 95% CI 18 to 29] of 204 participants) compared with placebo (35 [16%, 12 to 21] of 221; between-group difference –7% [95% CI –15 to 0]; p=0·066).

Interpretation Placebo was not non-inferior to azithromycin in terms of clinical improvement at day 5 in adults with lower respiratory tract infection and a low procalcitonin concentration. After accounting for both the rates of clinical improvement and solicited adverse events at day 5, it is unclear whether antibiotics are indicated for patients with lower respiratory tract infection and a low procalcitonin concentration.

Funding National Institute of Allergy and Infectious Diseases, bioMérieux.

Lancet Infect Dis 2022

Published Online December 13, 2022 https://doi.org/10.1016/S1473-3099(22)00735-6

See Online/Comment https://doi.org/10.1016/S1473-3099(22)00757-5

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Introduction

Lower respiratory tract infections are among the most common reasons for acute health-care visits.[1] Bacterial and viral lower respiratory tract infections have similar clinical manifestations resulting in high rates of inappropriate antibiotic use even in lower respiratory tract infection syndromes, such as acute bronchitis, where guidelines do not recommend antibiotics.[2,3] Although social and behavioural interventions have improved rates of inappropriate antibiotic use, such rates remain high.[3] Strategies are needed to identify patients unlikely to benefit from antibiotics, to mitigate the development and spread of resistant pathogens and reduce antibiotic-related adverse effects.

Procalcitonin is a host-derived inflammatory marker, and its expression correlates with the presence of bacterial infection and tracks with infection severity.[4,5] Procalcitonin-driven algorithms that recommend

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Research in context

Evidence before this study

Inappropriate prescribing of antibiotics for viral acute respiratory infection contributes to increased health-care costs and unnecessary drug-related adverse effects, and is a major contributor to antimicrobial resistance. This is among the reasons why developing improved diagnostics that can be applied in the outpatient setting has been recommended by numerous entities including WHO. As a complement to current pathogen-focused testing, host-based biomarkers can provide useful diagnostic information. This is predicated on the observation that patients respond differently to viral and bacterial infections. No biomarker has received more attention in this regard than procalcitonin. Procalcitonin was first described in the setting of sepsis, where concentrations were increased compared with non-infectious conditions. Moreover, procalcitonin has been used to distinguish bacterial infection from viral infection because interferon-γ production induced by viral infections inhibits procalcitonin production. However, studies assessing the performance characteristics in pneumonia revealed only moderate accuracy of procalcitonin to distinguish between bacterial and viral infections, with a 55% sensitivity and 76% specificity reported in a meta-analysis published by Kamat and colleagues (2020). Nevertheless, procalcitonin-guided management of lower respiratory tract infections has been used to withhold antibiotics or shorten the duration of antibiotic therapy without adversely affecting outcomes in several European studies. Specifically, low procalcitonin concentrations (≤0·25 ng/mL) were used to generate recommendations that antibiotics be withheld. Conversely, high procalcitonin concentrations prompted recommendations that antibiotics be provided. The results of these various studies are highlighted in a Cochrane database systematic review, which showed that antibacterial use decreased by 50% without adversely affecting clinical outcomes. However, the large, randomised, ProACT clinical trial in the USA did not observe antibiotic reductions when using a procalcitonin algorithm. Moreover, rates of adherence to the procalcitonin algorithm were variable and as low as 72·9% in the ProACT trial. Given these findings, it remains unclear whether low procalcitonin concentrations can be used to safely withhold antibiotics in patients with lower respiratory tract infection. We searched PubMed on Aug 15, 2022, with no date or language restrictions, using the terms "procalcitonin" and "clinical trial", and did not identify any results showing the clinical effect of an enforced procalcitonin algorithm. A search on the same date for "procalcitonin" and "placebo" on ClinicalTrials.gov identified one feasibility study involving randomisation to placebo in five participants, but results were not yet published.

Added value of this study

This randomised, placebo-controlled, double-blind, non-inferiority trial represents an approach to the evaluation of procalcitonin in lower respiratory tract infection that has not previously been evaluated. On the basis of the evidence from previous studies, we hypothesised that patients with suspected lower respiratory tract infection and a procalcitonin concentration of 0·25 ng/mL or less are unlikely to have a bacterial infection, and hence, would not benefit from antibiotics. Therefore, we hypothesised that treatment of these patients with placebo would be non-inferior to antibiotic treatment. By randomly assigning participants to antibiotics or placebo, this study design eliminated the possibility of algorithm non-adherence. We found that placebo was not non-inferior to azithromycin treatment in terms of clinical improvement at day 5. There was no increase in any adverse events among those treated with placebo. Later timepoints, including days 11 and 28, showed placebo to be non-inferior to azithromycin.

Implications of all the available evidence

The clinical community has long sought a means to identify which patients require antibiotic therapy and which can be safely managed without. Despite the abundance of procalcitonin-related literature, there is no consensus on its reliability in distinguishing bacterial infection from viral infection or guiding antibiotic use. The results of this study clarify many previous unknowns but do not address all scenarios. Specifically, this study excluded patients where the prescriber was unwilling to randomly assign the patient to placebo. Therefore, it remains unknown whether procalcitonin can safely and effectively guide antibiotic use on its own (independent of additional clinical information). These study results show that low procalcitonin concentrations in patients with lower respiratory tract infection are unable to identify when patients could benefit from azithromycin in terms of clinical improvement at day 5, possibly due to the drug's anti-inflammatory effects. At later timepoints, placebo was non-inferior to azithromycin. The placebo group also had lower rates of solicited adverse events and an intrinsically lower antibiotic use rate. Clinicians should weigh these factors (clinical improvement, reduced adverse events, and lower antibiotic use) when deciding whether to use procalcitonin as a guide for antibiotic initiation.

initiating or withholding antibacterials have been evaluated for safety and efficacy in multiple trials.[6–8] Results from these and other studies supported the 2017 US Food and Drug Administration (FDA) decision to clear procalcitonin as an aid in decision making on antibiotic use for inpatients or patients in the emergency department with lower respiratory tract infection.[9] A subsequent US-based study using the same algorithms, however, did not show a difference in antibiotic use compared with usual care.[10] Moreover, some antibiotics, such as azithromycin, have independent anti-inflammatory effects, which can mitigate lower respiratory tract infection symptoms.[11] A common feature of procalcitonin clinical trials conducted to date is that the algorithm recommends, but does not require, the specified therapeutic approach. This allows clinicians

to accommodate conflicting clinical data in deciding on antibiotic use. Because clinicians in these studies could over-rule the procalcitonin algorithm (as frequently as 56% of the time), previous studies do not directly address whether procalcitonin can identify a patient population for whom antibiotics offer no benefit, which is the assumption underlying its use.[6] The primary hypothesis of this study is that placebo is non-inferior in efficacy to azithromycin in terms of clinical improvement in adults with suspected lower respiratory tract infection and a procalcitonin concentration of 0·25 ng/mL or less. We aimed to compare the efficacy and safety of azithromycin versus placebo to treat lower respiratory tract infections in patients with low procalcitonin.

Methods

Study design

We conducted a randomised, placebo-controlled, double-blind, non-inferiority trial (TRAP-LRTI) at five health centres in the USA (Atlanta Veterans Affairs Health Care System [VAHCS], Hope Clinic of Emory University, Duke University Hospital, Durham VAHCS, and Michael E DeBakey Veterans Affairs Medical Center). The trial was approved by the institutional review board at each site. Written informed consent was obtained from participants before any study procedures. An independent data safety monitoring board provided safety oversight. The protocol is available at https://www.clinicaltrials.gov/ProvidedDocs/73/NCT03341273/Prot_000.pdf.

Participants

Participants were enrolled at outpatient clinics and emergency departments. None of the sites used procalcitonin as part of routine lower respiratory tract infection management.

Adults aged 18 years or older with clinically suspected non-pneumonia lower respiratory tract infection and symptom duration from 24 h to 28 days were eligible for enrolment. Inclusion required at least two qualifying patient-reported symptoms or one qualifying symptom and at least one qualifying vital sign. Qualifying symptoms were new or worsening cough, new sputum production, increased volume or purulence of chronic sputum production, chest pain, and difficulty breathing. Qualifying vital signs were temperature of 37·8°C or greater or patient-reported fever, heart rate of 90 beats per min or greater, or respiratory rate of greater than 20 breaths per min. Exclusion criteria were hospitalisation before enrolment, known or suspected infection at other anatomical sites requiring antibacterial therapy, known or suspected pneumonia based on chest imaging and clinical diagnosis, immunosuppression, azithromycin use in the past 2 weeks or any systemic antibiotic in the past 24 h, contraindication to azithromycin use, and any condition that in the opinion of the referring provider or site investigator precluded participation in the trial. The type of lower respiratory tract infection (eg, acute bronchitis, asthma exacerbation, or acute exacerbation of chronic obstructive pulmonary disease) was not recorded because of imprecision in the diagnostic criteria and overlapping clinical syndromes.[12]

Randomisation and masking

Participants had serum or plasma collected for procalcitonin measurement within 2 h of enrolment using the Vidas BRAHMS PCT according to manufacturer instructions (bioMérieux, Marcy-l'Étoile, France). All other clinical evaluations including laboratory testing and radiography were performed at the treating clinician's discretion. At enrolment, a nasopharyngeal swab was collected and banked for subsequent batched testing by the Respiratory Panel 2 (BioFire Diagnostics, Salt Lake City, UT, USA). Participants with a procalcitonin concentration of 0·25 ng/mL or less were randomly assigned (1:1), in blocks of four with stratification by site, to receive over-encapsulated oral azithromycin 250 mg or matching placebo (two capsules on day 1 followed by one capsule daily for 4 days). The Emmes Corporation generated treatment numbers for pill bottles, which were shipped to sites in multiples of six (three placebo, three azithromycin). After study staff confirmed eligibility, Emmes assigned a treatment number for the pharmacist to dispense. The first dose was to be taken within 24 h of randomisation. Participants, non-study clinical providers, investigators, and study coordinators were masked to treatment allocation.

Procedures

We performed a post-hoc analysis to assess the potential mechanisms by which azithromycin affected clinical outcomes. Ten cytokines (interferon [IFN]-γ, interleukin [IL]-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and tumor necrosis factor [TNF]-α) were measured in duplicate by the Biomarkers Core Facility at the Duke Molecular Physiology Institute using the manufacturer's protocol (VPLEX PLUS Proinflammatory Panel 1, Meso Scale Diagnostics, Rockville MD) for participants with plasma available at days 1 and 5.

Outcomes

The primary outcome was the efficacy of azithromycin versus placebo in terms of clinical improvement at day 5. Clinical improvement was defined as improvement in two or more qualifying patient-reported symptoms (or improvement in one symptom and one vital sign abnormality); no deterioration in any qualifying symptom nor new vital sign abnormality; absence of fever in the 24 h before the day 5 visit; and no medically attended visits for persistent or worsening lower respiratory tract infection requiring antibacterial therapy. Absence of fever at day 5 was based on participants' measurement of their temperatures using a study-provided thermometer in the preceding 24 h as well as temperature measurement by study staff at the day 5 in-person visit. This efficacy

definition was selected because of its use in previous studies.[13] Secondary outcomes included the individual efficacy components for azithromycin versus placebo at days 11 and 28. The composite efficacy outcome to determine non-inferiority was added during a protocol amendment on July 24, 2018. Secondary outcomes also compared azithromycin to placebo in terms of Response Adjusted for Days of Antibiotic Risk (RADAR).[14] RADAR was determined by categorising each participant's clinical outcome according to a Desirability of Outcome Ranking (DOOR), an 8-level ordinal clinical outcome encompassing three components: clinical improvement, the presence of patient-reported antibiotic-related solicited adverse events (abdominal pain, vomiting, diarrhoea, allergic reactions, and candidiasis), and their severity (mild, moderate, or severe; appendix p 2).[14] For RADAR, the desirability of the overall patient experience was further ranked by the observed treatment duration (not treatment assignment) with fewer days of antibiotic use receiving a more desirable rank. Post-hoc subgroup analyses were performed to explore treatment interactions by baseline characteristics, selected due to the possible contributions they might make to the underlying lower respiratory tract infection or its response to treatment. This analysis was performed in a similar manner to the primary analysis: we fit a linear regression model on clinical improvement at the day 5 visit for each level of the subgroup variable while adjusting for the actual day of the day 5 visit and ignoring missing data. An interaction test was performed to assess whether the effect of treatment was different among the categories of the subgroup analysis; this was performed for the day 11 visit as well. Additional secondary and exploratory endpoints are listed in the statistical analysis plan, which is available at ClinicalTrials.gov, and the appendix (pp 12–13).

See Online for appendix

Statistical analysis

The study planned to enrol 840 participants, to randomly assign 420 (210 per group), with 80% power at a 2·5% significance level for a one-sided hypothesis to show non-inferiority of placebo to azithromycin with a –12·5% non-inferiority margin, assuming a day 5 clinical improvement rate of 80%. The size of the non-inferiority margin was chosen to match existing FDA guidance for the study of community-acquired bacterial pneumonia.[15] Although patients known to have bacterial pneumonia were excluded from this study, the FDA guidance document offered a well-established precedent for other types of lower respiratory tract infection studied here. At a planned interim analysis, assumptions underlying the targeted sample size were assessed, resulting in a recalculated sample size of 674 enrolled participants, to randomly assign 560 for the per-protocol analysis, given an observed day 5 clinical improvement rate of 58% (102 of 177 participants). Because of the COVID-19 pandemic, enrolment closed with 514 participants enrolled and 499 randomly assigned, resulting in 77% power.

The primary analyses were conducted using an intention-to-treat approach, including all participants who were randomly assigned. Baseline characteristics in the two treatment groups were reported using frequency distributions and descriptive statistics. As recommended by FDA guidance,[16] assessment of non-inferiority at the day 5 primary endpoint used a two-sided 95% CI of the difference in the rates (placebo group–azithromycin group), with non-inferiority of placebo compared with azithromycin concluded if the lower limit of the 95% CI was less than the non-inferiority margin of –12·5%. If non-inferiority was concluded, it could be interpreted that azithromycin treatment would be unnecessary. Wald type CIs were calculated on the basis of the proportions from a linear regression with multiple imputation and adjustment for the actual day of the study visit (because study visits could occur within a predefined window) in the final model. Assuming a missing-at-random process, multiple imputation methodology with linear regression was used to impute missing primary outcomes for the intention-to-trear population. A per-protocol analysis was conducted to evaluate the robustness of the results from the intention-to-treat analysis. Per-protocol analyses by definition required complete data and so did not require imputation. Similar analyses were conducted for days 11 and 28. For all analyses, rates and differences in rates of clinical improvement were estimated from linear regression, adjusting for the actual day of the designated study visit (eg, the day 5 visit could occur on days 5, 6, 7, or 8), instead of being calculated directly from absolute numbers.

The DOOR, a key secondary endpoint, was analysed by the RADAR method.[14] When calculating the probability of having a more desirable outcome with placebo than with azithromycin (Wilcoxon-Mann-Whitney statistic) as a summary contrast measure, the probability was adjusted by the number of observed days of antibiotic as a tie-breaker, where a shorter duration of antibiotic use was considered more desirable when comparing participants with the same DOOR rank. The unadjusted probabilities were also calculated. Given the composite nature of the DOOR, its individual components were analysed separately using similar methods.

Cytokine measurements of less than the lower limit of detection were imputed at half of the lower limit. Multiplicity for cytokine data analyses were adjusted using Holm's procedure.[17] All analyses were conducted using SAS (version 9.4) or R (version 3.2 or later).

This trial is registered with ClinicalTrials.gov, NCT03341273.

Role of the funding source

The National Institute of Allergy and Infectious Diseases and Antibacterial Resistance Leadership Group were involved in the study design, data collection, data analysis, data interpretation, and writing of the report. bioMérieux provided study product (azithromycin and placebo) and instruments and reagents to perform procalcitonin and

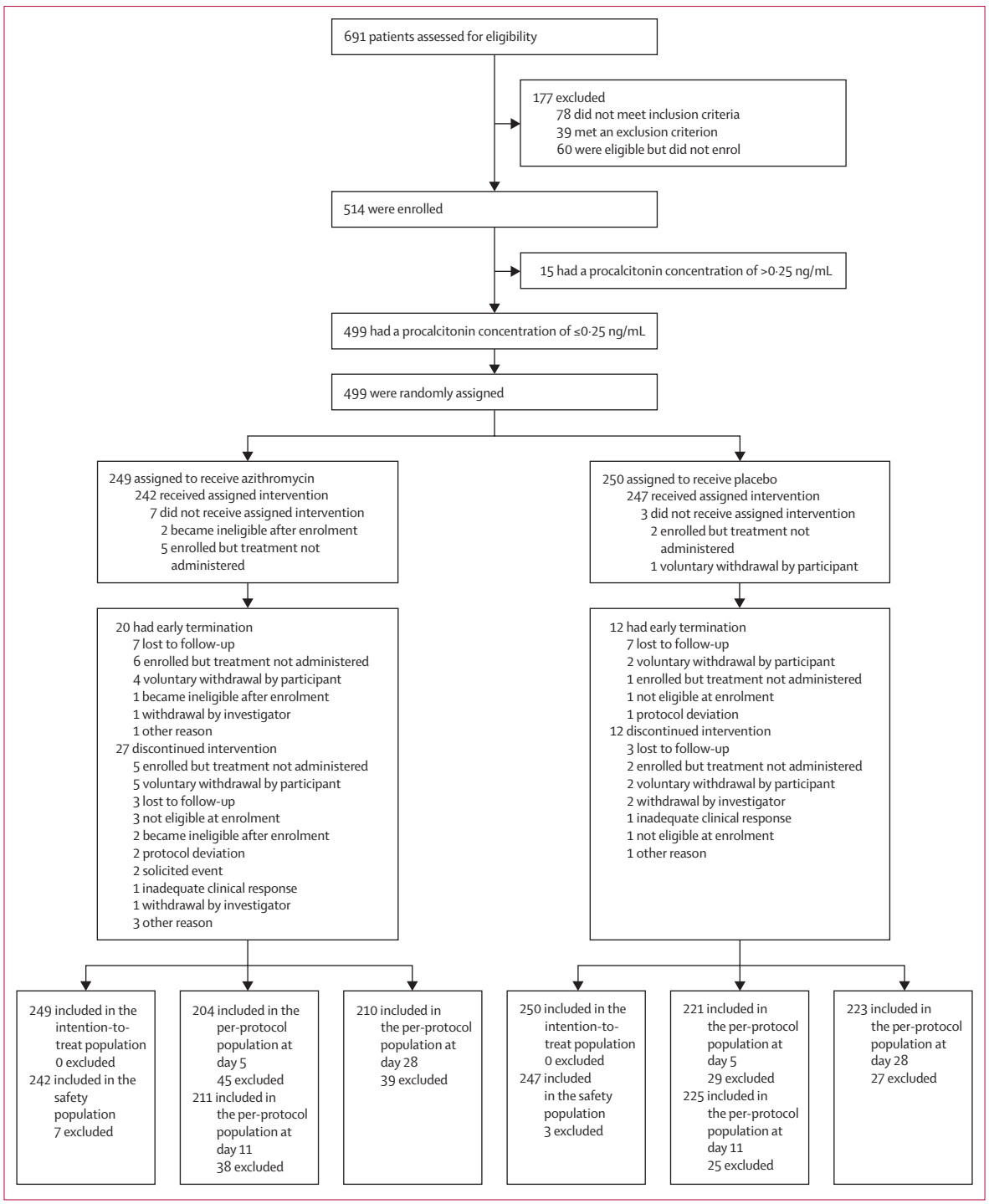

Figure 1: **Trial profile**

Respiratory Panel-2 testing, and provided input on study conception and design, but had no role in the decision to publish these results. One bioMerieux employee is a co-author and therefore offered critical review of the manuscript. bioMerieux did not otherwise participate in any analysis or writing of the paper.

Results

Between Dec 8, 2017, and March 9, 2020, 691 patients were assessed for eligibility, 514 were enrolled, and 499 with a procalcitonin concentration of 0·25 ng/mL or less were randomly assigned to receive azithromycin (n=249) or placebo (n=250) and were included in the

	Azithromycin group (n=249)	Placebo group (n=250)
Age, years	52·8 (15·9)	51·7 (15·0)
Sex		
Male	169 (68%)	154 (62%)
Female	80 (32%)	96 (38%)
Race		
White	81 (33%)	89 (36%)
Black or African American	159 (64%)	146 (58%)
Asian	4 (2%)	1 (<1%)
American Indian or Alaska Native	0	3 (1%)
Native Hawaiian or Other Pacific Islander	0	1 (<1%)
Multiracial	2 (<1%)	8 (3%)
Unknown	3 (1%)	2 (<1%)
Ethnicity		
Not Hispanic or Latino	228 (92%)	233 (93%)
Hispanic or Latino	17 (7%)	16 (6%)
Unknown	4 (2%)	1 (<1%)
Pre-existing medical conditions*		
Any	225 (90%)	230 (92%)
Vascular	136 (55%)	112 (45%)
Metabolic	118 (47%)	108 (43%)
Respiratory	102 (41%)	116 (46%)
Psychiatric	66 (27%)	69 (28%)
Gastrointestinal	54 (22%)	64 (26%)
Musculoskeletal or connective tissue	58 (23%)	56 (22%)
Baseline lower respiratory tract infection symptoms or signs		
Chest pain	151 (61%)	157 (63%)
Cough	243 (98%)	245 (98%)
Difficulty breathing	177 (71%)	182 (73%)
Fever	117 (47%)	115 (46%)
Sputum production	219 (88%)	205 (82%)

Data are mean (SD) or n (%). *Only pre-existing condition categories with greater than 15% prevalence are listed.

Table 1: **Baseline characteristics of the intention-to-treat population**

	Participants with clinical improvement	Between-group difference	Non-inferiority*
Day 5			
Intention-to-treat population			
Azithromycin group (n=249)	155 (69% [61 to 77])	..	..
Placebo group (n=250)	148 (63% [54 to 71])	–6% (–15 to 2)	No
Per-protocol population			
Azithromycin group (n=204)	136 (70% [62 to 79])	..	..
Placebo group (n=221)	136 (65% [57 to 74])	–5% (–14 to 4)	No
Day 11			
Intention-to-treat population			
Azithromycin group (n=249)	187 (81% [74 to 87])	..	..
Placebo group (n=250)	184 (76% [70 to 83])	–4% (–12 to 3)	Yes
Per-protocol population			
Azithromycin group (n=211)	174 (80% [73 to 87])	..	..
Placebo group (n=225)	177 (77% [70 to 83])	–4% (–11 to 4)	Yes
Day 28			
Intention-to-treat population			
Azithromycin group (n=249)	202 (88% [83 to 93])	..	..
Placebo group (n=250)	194 (82% [77 to 86])	–7% (–13 to 0)	No
Per-protocol population			
Azithromycin group (n=210)	185 (88% [83 to 93])	..	..
Placebo group (n=223)	184 (82% [77 to 87])	–6% (–12 to 1)	Yes

Data are n (% [95% CI]) or % (95% CI). *Non-inferiority of placebo was concluded if the lower bound of the 95% CI for the between-group difference in proportions was greater than –12·5%.

Table 2: **Rates of clinical improvement by timepoint and analysis population**

intention-to-treat population (figure 1). The per-protocol population ranged from 204 to 211 participants in the azithromycin group and from 221 to 225 in the placebo group, depending on the timepoint (day 5, 11, or 28). Baseline characteristics were similar in the two groups (table 1). The majority of participants were Black (305 [61%] of 499), non-Hispanic (461 [91%]), and male (323 [65%]), with a mean age of 52 years (median 55 years, range 18–93). Six patients (two in the azithromycin group and four in the placebo group) had taken non-azithromycin antibiotics between 24 h and 2 weeks before enrolment. Pre-existing medical conditions were reported in 91% of all participants and were similar in frequency between the two groups. 158 (32%) of 499 participants had asthma and 57 (11%) had chronic obstructive pulmonary disease. All five doses of study product were taken by 221 (89%) of 249 participants in the azithromycin group and 237 (95%) of 250 in the placebo group. In the intention-to-treat population, routine clinical testing and supplemental multiplex respiratory pathogen testing identified seven participants with bacterial infections and 261 with viral infections (54% of the cohort). These were evenly distributed between the placebo (three bacterial and 133 viral) and azithromycin (four bacterial and 128 viral) groups. The bacterial pathogens included *Mycoplasma pneumoniae* (n=2), *Streptococcus pyogenes* (n=2), *Chlamydia pneumoniae* (n=1), *Haemophilus influenzae* (n=1), and *Bordetella parapertussis* (n=1). The most frequently detected viruses were rhinovirus or enterovirus (n=99) and influenza (n=76).

The primary outcome of clinical improvement at day 5 was observed in 148 (63%, 95% CI 54 to 71) of 238

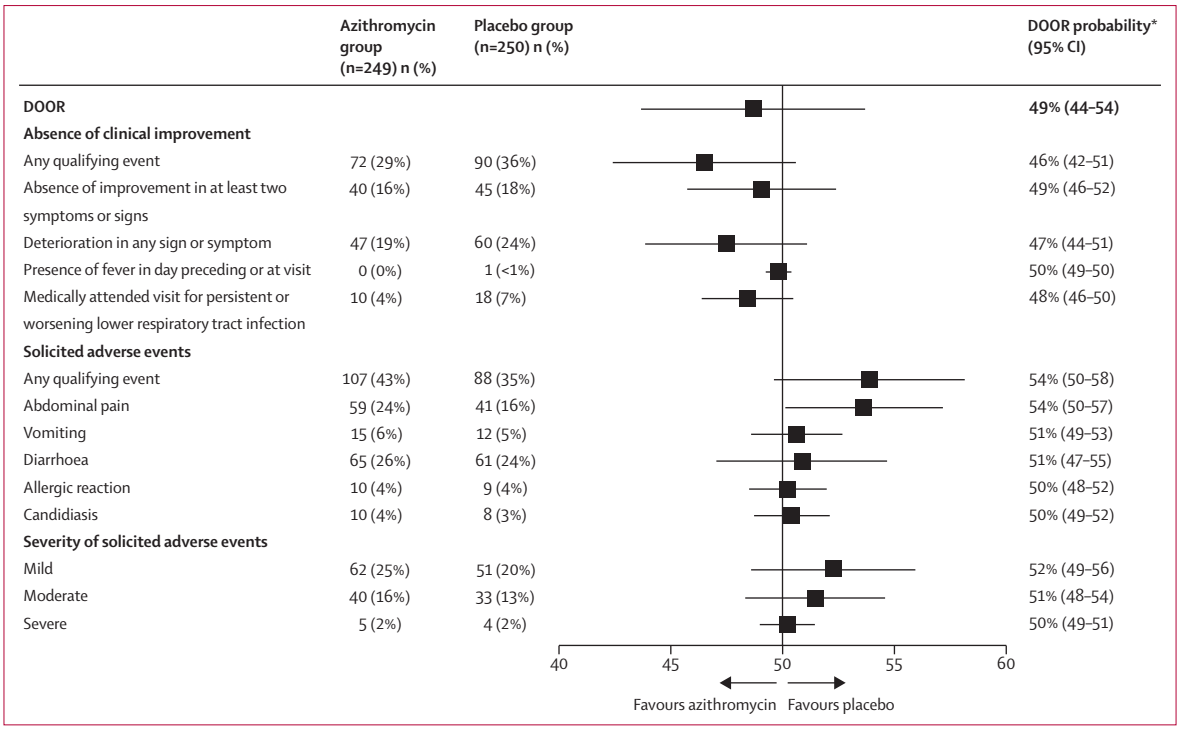

Figure 2: **Clinical improvement and solicited adverse events at day 5**
The DOOR incorporates elements of clinical improvement and solicited adverse events while simultaneously considering the severity of those adverse events. Presented values indicate the probability of a more desirable DOOR when assigned to placebo versus azithromycin; probabilities of greater than 50% indicate a more favourable DOOR with placebo. Rather than reporting probabilities of adequate clinical improvement (a study endpoint), we report its absence to align the treatment-dependent directionality shown. Error bars show 95% CI. DOOR=desirability of outcome ranking.

participants with full data in the placebo group and 155 (69%, 61 to 77) of 227 participants with full data in the azithromycin group in the intention-to-treat analysis (between-group difference –6%, 95% CI –15 to 2; table 2). Because the lower bound of this difference was less than –12·5%, non-inferiority of placebo compared with azithromycin could not be concluded. In the per-protocol analysis, clinical improvement at day 5 was observed in 136 (65%, 95% CI 54 to 74) of 221 participants in the placebo group and 136 (70%, 62 to 79) of 204 in the azithromycin group (between-group difference –5%, 95% CI –14 to 4), so non-inferiority could not be concluded. Although placebo was not non-inferior to azithromycin at day 5, there was no significant difference in the rates of any of the individual parameters comprising the clinical improvement composite outcome (figure 2).

In the intention-to-treat analysis, clinical improvement at day 11 was observed in 184 (76%, 95% CI 70 to 83) of 235 participants in the placebo group and 187 (81%, 74 to 87) 226 in the azithromycin group (between-group difference –4%, 95% CI –12 to 3), so non-inferiority of placebo compared with azithromycin was shown (table 2). The per-protocol analysis at day 11 showed similar results (table 2). Although placebo was non-inferior to azithromycin in clinical improvement at day 11, the placebo group had higher rates than the azithromycin group of worsening sputum production (14 [6%, 95% CI 4 to 10] of 225 participants *vs* three [1%, 1 to 4] of 211; between-group difference 5%, 95% CI 1 to 9; p=0·012) and worsening difficulty breathing (eight [4%, 2 to 7] *vs* one [<1%, <1 to 3]; between-group difference 3%, 1 to 6; p=0·038).

Results at day 28 were mixed: the intention-to-treat analysis did not show non-inferiority of placebo compared with azithromycin in terms of clinical improvement at day 28 (194 [82%] of 238 participants *vs* 202 [88%] of 229, between-group difference –7%, 95% CI –13 to 0), but the per-protocol analysis indicated non-inferiority (between-group difference –6%, –12 to 1; table 2).

DOOR rankings incorporate clinical improvement and adverse events (appendix pp 2–3). The probability of a more desirable rank when assigned to placebo was 49% (95% CI 44 to 54) for DOOR (figure 2) and 62% (95% CI 56 to 67) for RADAR at day 5, and 51% (46 to 56) for DOOR (appendix p 4) and 65% (60 to 70) for RADAR at day 11. Individual elements of clinical improvement, solicited adverse events, and the severity of solicited adverse events were not significantly different between groups at day 5, except for increased abdominal pain associated with azithromycin treatment (47 [23%, 95% CI 18 to 29] of 204 participants) compared with placebo (35 [16%, 12 to 21] of 221; between-group difference

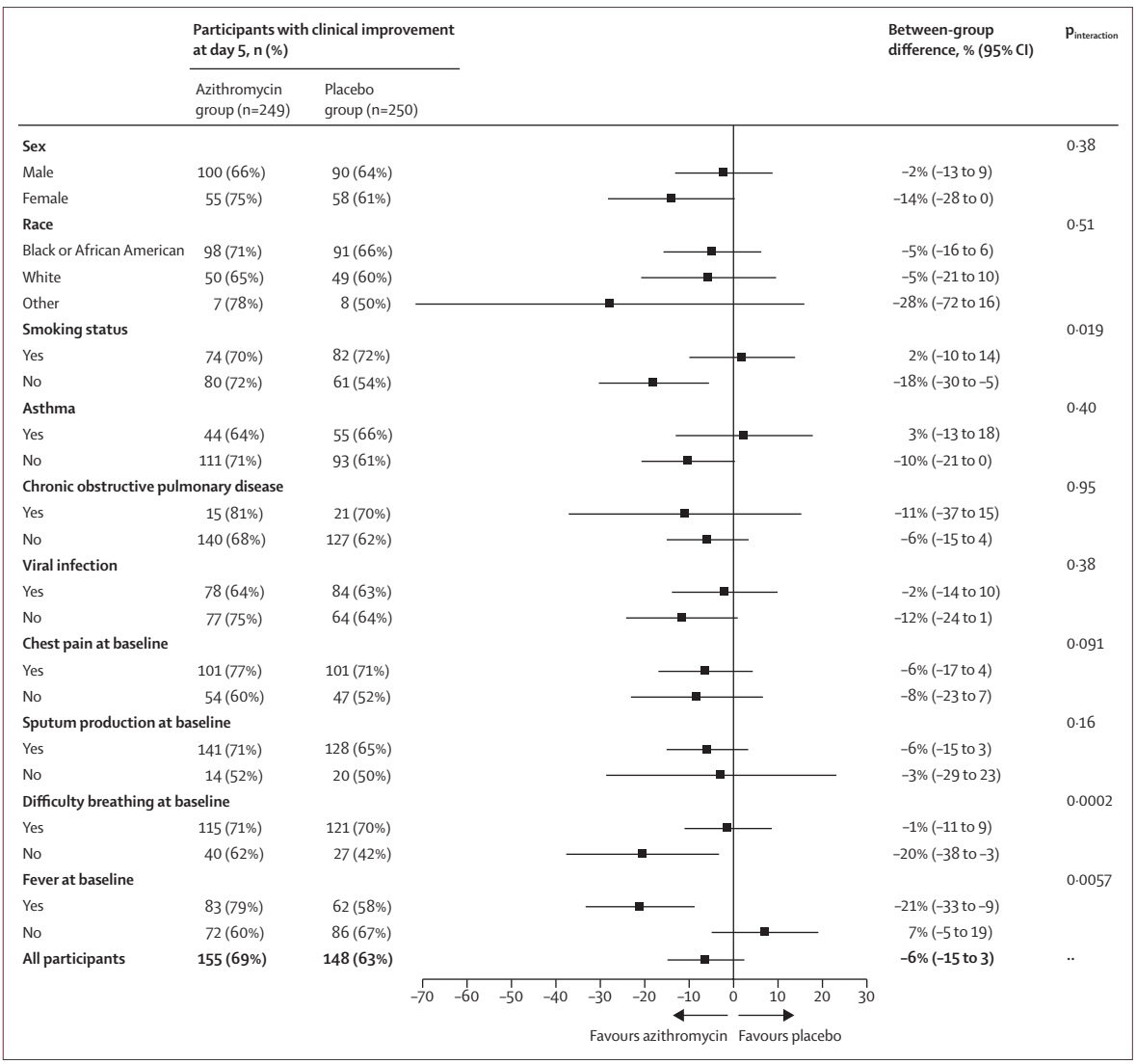

Figure 3: **Forest plot of clinical improvement at day 5 by baseline characteristics in the intention-to-treat population**
Each point estimate and error bars represent the estimate of the between-group difference in rates of clinical improvement at day 5 and the associated 95% CI obtained from a linear regression model. A between-group difference of greater than 0 favours azithromycin. Interaction p values are obtained from an interaction Type III test, where the interaction term between subgroup variable and treatment is being added to the linear regression model.

–7% [95% CI –15 to 0]; p=0·066). No participants died. Four participants (three in the placebo group and one in the azithromycin group) were hospitalised for persistent or worsening lower respiratory tract infection in the intention-to-treat population, although none required intensive care unit admission.

In the post-hoc analysis of change in concentrations of ten cytokines from enrolment to day 5, samples were available at both timepoints for 374 participants (172 in the azithromycin group and 202 in the placebo group). IL-1β, IL-2, IL-4, IL-12p70, and IL-13 had high rates of undetectable concentrations (68–94% of samples) and were excluded from analysis. By contrast, IFN-γ, IL-6, IL-8, IL-10, and TNF-α had undetectable concentrations in only 0–2% of samples. The changes in cytokine levels from enrolment to day 5 were not signficantly different when stratified by clinical improvement (appendix p 5). However, IL-8 showed significantly greater declines in the azithromycin group than in the placebo group (median change –1·5 pg/ml [IQR –3·4 to 0·0] *vs* –0·4 pg/ml [–2·8 to 1·9]; p=0·0019). Moreover, this difference was only significant among participants with clinical improvement (median change –1·8 pg/ml [IQR –4·0 to –0·1] for azithromycin *vs* –0·9 pg/ml [–2·7 to 1·2] for placebo; p=0·0036; appendix p 6). No treatment-related differences in IL-8 were observed among participants without clinical improvement (median change –1·1 pg/ml [IQR –2·3 to 0·3] for azithromycin *vs* 0·1 pg/ml [–2·8 to 2·5] for placebo; p=0·099).

No pre-existing medical conditions or concomitant medications were associated with clinical improvement at days 5 or 11 (appendix pp 7–8). In a post-hoc analysis, logistic regression identified participants who reported difficulty breathing at enrolment as more likely to have clinical improvement than those who did not report difficulty breathing at enrolment, with an odds ratio of 2·29 (95% CI 1·40–3·73) at day 5 (appendix p 9) and 2·24 (1·25–4·00) at day 11 (appendix p 10). In a second post-hoc analysis, no significant treatment-dependent associations with clinical improvement were observed for sex, race, pre-existing asthma, pre-existing chronic obstructive pulmonary disease, identification of a viral cause, chest pain at enrolment, or sputum production at enrolment. However, a significant treatment effect was observed in participants with or without difficulty breathing at enrolment, as well as in participants with or without fever at enrolment (figure 3). Participants without difficulty breathing at enrolment had higher rates of clinical improvement in the azithromycin group (62%) than in the placebo group (42%; p=0·0002 for the interaction of difficulty breathing and treatment). Participants with fever at enrolment had higher rates of clinical improvement in the azithromycin group (79%) than in the placebo group (58%; p=0·0057 for the interaction of fever and treatment). Similar results were seen at day 11 (appendix p 11). There was also a significant treatment effect among participants who did not smoke and a significant interaction between treatment effect and smoking status, but this was only present at day 5 (p=0·019 for the interaction of smoking status and treatment; figure 3) and not at day 11 (p=0·41; appendix p 11).

Discussion

Procalcitonin is a host response biomarker used to guide antibiotic prescribing in patients with lower respiratory tract infection on the basis of its ability to discriminate between bacterial infection and other diseases. The studies supporting this indication were randomised clinical trials of a procalcitonin-based algorithm to recommend administering or withholding antibiotics, which clinicians adhered to at rates of 44–97% across 18 trials.[6] Furthermore, procalcitonin-based algorithms were associated with variable decreases in antibiotic use, with some studies showing no effect.[10] Consequently, uncertainty persists as to whether a low procalcitonin concentration can identify patients for whom anti-bacterials can be safely withheld. To answer this question, we conducted the TRAP-LRTI trial, which aimed to evaluate whether a low procalcitonin concentration can identify adults with non-pneumonia lower respiratory tract infection who would derive no benefit from azithromycin compared with placebo. This non-inferiority trial had no algorithm or treatment recommendation. Instead, participants with low procalcitonin concentrations were randomly assigned to receive azithromycin or placebo, to observe whether placebo would be non-inferior in these patients. At the early day 5 endpoint, we could not conclude that placebo was non-inferior to azithromycin., However, there was no individual component of the composite endpoint that significantly differed between groups; including no increase in patient harm as measured by medically attended visits, hospitalisation, intensive care unit admission, or death. The failure to show non-inferiority might have been affected by the premature termination of enrolment due to COVID-19 and decreased power (77% compared with the planned 80%). However, at later timepoints, when recovery from viral infection was expected,[18,19] placebo was non-inferior to azithromycin on day 11, and day 28 in the per-protocol analysis. DOOR, a global patient outcome based on clinical benefits and harms,[14] showed no significant difference between treatment groups, although azithromycin was associated with more solicited adverse events, particularly abdominal pain. RADAR extends the DOOR outcome by accounting for antibiotic use. In doing so, we observed superiority of placebo over azithromycin, primarily due to reduced antibiotic use in the placebo group.

This study's primary endpoint of 5 days was chosen on the basis of established treatment endpoints for community-acquired bacterial pneumonia and to identify clinical deterioration due to absence of required antibacterial treatment.[15] However, we observed rates of clinical improvement that were lower at 5 days than would be expected for community-acquired bacterial pneumonia, consistent with the largely viral nature of lower respiratory tract infection observed in this study. Additionally, higher rates of clinical improvement in the azithromycin group could have been due to the drug's anti-inflammatory effects rather than its antibacterial properties. Azithromycin lowers cytokine responses, most notably IL-8, which is elevated in respiratory viral infections.[11,20–23] These anti-inflammatory properties of azithromycin supported its selection over other antibiotics. For example, placebo showing non-inferiority compared with an antibiotic such as amoxicillin could have left persistent questions about whether antibiotics with anti-inflammatory properties, such as azithromycin, would have produced different results. Azithromycin is also a guideline-recommended antibiotic for the treatment of acute exacerbations of chronic obstructive pulmonary disease associated with bacterial triggers.[24] To further explore the anti-inflammatory properties of azithromycin, we measured concentrations of multiple inflammatory cytokines at enrolment and day 5 to assess treatment-related cytokine changes. We observed decreases in IL-8 among participants in the azithromycin group, which was only significant in participants who had clinical improvement. This is consistent with the hypothesis that azithromycin-associated reductions in IL-8 could contribute to the higher day 5 clinical improvement rates. A common clinical manifestation of

inflammation is fever. An exploratory analysis suggested that participants with fever were more likely to have clinical improvement when treated with azithromycin than with placebo. This finding might suggest that fever should prompt antibacterial therapy, although fever is a poor discriminator between bacterial and viral infections. The results of this study do not distinguish whether it is the antibacterial, anti-inflammatory, or both properties of azithromycin that explain this observation. They also do not address whether procalcitonin identifies patients who might benefit from anti-inflammatory therapy. Additional research, specifically in patients with fever, would help address this question.

Previous studies using a procalcitonin algorithm included diverse populations spanning children to adults, colds to pneumonia, and outpatients to the critically ill.[8,10,25–27] This study focused on outpatient adults enrolled in clinics or emergency departments who had non-pneumonia lower respiratory tract infection. We excluded cases of pneumonia to minimise risks to participants and because previous evidence showed that reductions in antibiotics using procalcitonin algorithms were greatest in non-pneumonia lower respiratory tract infection.[7] The cohort had few participants with increased procalcitonin concentrations, suggesting that there might have been some bias in participant selection. We also did not categorise the type of lower respiratory tract infection (eg, acute bronchitis, asthma exacerbations, or acute exacerbations of chronic obstructive pulmonary disease) because of imprecision in the diagnostic criteria and overlapping clinical syndromes. This is underscored by persistently high rates of inappropriate antibiotic use in patients with syndromes for whom antibiotics are not otherwise recommended.[3] As such, we were unable to determine if particular subtypes of lower respiratory tract infection are more suitable for a procalcitonin-driven strategy. No pathogen was identified in 46% of the cohort, raising the possibility that some participants did not have an infection at all and representing another opportunity to limit unnecessary antibiotic use.

Future procalcitonin studies (or those of other biomarkers) should consider a similar design to this trial, in which participants were randomly assigned to antibiotic or placebo therapy when a bacterial infection was unlikely. In particular, studies of other acute respiratory infections, such as pneumonia, as well as other age groups, such as infants and children, would be an important extension of this study.

The study limitations include that most screened participants had low procalcitonin concentrations and there was a low prevalence of bacterial infection. It is unclear how well this represents a typical population with non-pneumonia lower respiratory tract infection. The study did not address the use of procalcitonin in patients with pneumonia or immunocompromise, who were excluded from this trial. Lower respiratory tract infection was not further stratified into conditions where antibiotics are routinely or occasionally prescribed (eg, acute exacerbation of chronic obstructive pulmonary disease *vs* acute bronchitis). We did not compare or combine multiple diagnostic approaches (eg, host gene expression testing or microbial testing) with procalcitonin.[28,29] Another antibiotic without notable anti-inflammatory properties could have been chosen. However, azithromycin is a frequently prescribed antibiotic for non-pneumonia lower respiratory tract infection, in part because of its pleiotropic effects.[30] Furthermore, we cannot assume that similar results would have been observed using an antibiotic with a different spectrum of activity to azithromycin. All of the bacterial pathogens identified in this study are generally susceptible to azithromycin. However, it is possible we enrolled (but did not identify) patients with azithromycin-resistant infections, which would have lowered rates of clinical improvement in both groups. The study did not achieve the prespecified target enrolment due to the COVID-19 pandemic, although the study still had 77% power to show non-inferiority, compared with the planned 80%. The study's primary endpoint was based on day 5 clinical improvement, which was likely to be too early given the viral cause of infection in most cases.

In conclusion, placebo was not non-inferior to azithromycin in terms of clinical improvement at day 5 for adults with non-pneumonia lower respiratory tract infection and a low procalcitonin concentration, but was non-inferior at day 11 and showed mixed findings at day 28. However, the placebo group showed better outcomes using a RADAR analysis that accounted for azithromycin-related solicited adverse events and the inherent harms of unnecessary antibiotic use. Furthermore, patients with non-pneumonia lower respiratory tract infection have high rates of clinical improvement through 28 days, regardless of antibacterial treatment.

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Contributors

ELT, NGR, RTS, MCR-B, DMW, CWW, GKS, EBW, HMES, SRE, WAK, VG, MSL, and EL conceived and designed the study. ELT, NGR, RTS, MCR-B, MTM, BJB, DW, DMW, MJM, GA, JJZ, NM, CSK, DLR, SHB, NB, JJW, MEK, MHC, AWD, ARB, LO, ZY, and ERK contributed to the collection of data. BT, ES, LZ, WD, TH, and SRE performed the analysis. BT and ES accessed and verified all the data. ELT, NGR, BT, ES, and SRE wrote the manuscript. All authors critically reviewed the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

ELT and CWW report consulting for Biomeme. ELT, CWW, and MTM have a patent pending for Methods to Diagnose and Treat Acute Respiratory Infections (US20180245154A1). Following completion of the study, ELT became an employee of Danaher Diagnostics. EBW is a principal investigator for Pfizer-funded studies of COVID-19 vaccine, a co-investigator for a vaccine study funded by Moderna, and a member of an advisory board for Vaxcyte. NGR serves as a safety consultant for the Emmes Corporation and ICON-I, and reports research funds from Pfizer, Merck, Sanofi, Quidel, and Lilly. All other authors declare no competing interests.

Data sharing

Individual deidentified participant data (and supporting documentation, data dictionaries, and protocol) that underlie the results in this Article can be made available to investigators following submission of a plan for data use, approval by the Antibacterial Resistance Leadership Group (ARLG) or designated entity, and execution of required institutional agreements. Provision might be contingent upon the availability of funding for data preparation and deidentification. More information can be found at https://arlg.org/how-to-apply/requestdata/. The full protocol and statistical analysis plan can be accessed at https://www.clinicaltrials.gov/ct2/show/NCT03341273.

Acknowledgments

This project was funded in part by the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, Department of Health and Human Services, under contracts to the Vaccine and Treatment Evaluation Units at Duke University (HHSN272201300017I, principal investigator EBW), Emory University (HHSN272201300018I, principal investigator NGR) and Baylor College of Medicine (HHSN27220130015I, principal investigator HMES). Additional support was provided by NIAID award UM1AI104681 to the ARLG. bioMérieux provided study product (azithromycin and placebo), instruments, and reagents to perform procalcitonin and Respiratory Panel-2 testing, and provided input on study conception and design. Statistics and data management support for the trial was provided by the EMMES corporation under NIAID award HHSN272201500002C. RTS was supported by grants from the National Institute of Health (R01HL144478) and the Department of Veterans Affairs (VA MR BX001786). We would like to acknowledge the study participants, the institutions that contributed to participant recruitment, members of the Data and Safety Monitoring Board (David Carlin, Eric Meissner, Emanuel Rivers, Eugene Shapiro, and Ellen Wald), bioMérieux (Samuel Bozzette), and the following individuals who supported the TRAP-LRTI study: Dilshad Rafi Ahmed, Mary Bower, Ana Drobeniuc, Lisa Harewood, Christopher Huerta, Jessica Ingersoll, Jesse Jacob, Brandi Johnson, Colleen Kelley, Dean Kleinhenz, Lilin Lai, Pamela Lankford-Turner, Hollie Macenczak, Michele McCullough, Candace Miller, Juliet Morales, Varun Phadke, Youssef Saklawi, Amy Sherman, Taé Stallworth, Jessica Traenkner, Cynthia Whitney, and Zanthia Wiley (Emory University and Atlanta VA Health Care System); Jack Anderson, Brian Antczak, Luis Ballon, Thomas Burke, Katherine Frankey, Joyce Gandee, Kristen Gunnell, Lynn Harrington, Sara Hoffman, Pearce Jackson, Ally Johnson, Alexander Limkakeng, Tyffany Locklear, Anna Mazur, Beth McLendon-Arvik, Ellen Poulsen, Cathy Sampey, Liz Schmidt, Stephanie Smith, and Rachel Toler (Duke University and Durham VA Health Care System); Katharine Breaux, Biju Johnson, Bashir Lengi, Dena Mansouri, and Tehquin Tanner (Michael E DeBakey VA Medical Center); Jane Knisley and Janie Russell (Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Disease, National Institutes of Health); and Tom Conrad, Aya Nakamura, Randolph Oler, Michelle Serock, Alison Wall, and Katie Wiegand (Emmes Corporation).

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Tsalik EL, Rouphael NG, Sadikot RT, et al. Efficacy and safety of azithromycin versus placebo to treat lower respiratory tract infections associated with low procalcitonin: a randomised, placebo-controlled, double-blind, non-inferiority trial. *Lancet Infect Dis* 2022; published online Dec 13. https://doi.org/10.1016/S1473-3099(22)00735-6.

Efficacy and safety of azithromycin versus placebo to treat lower respiratory tract infections associated with low procalcitonin: a randomised, placebo-controlled, double-blind, non-inferiority trial

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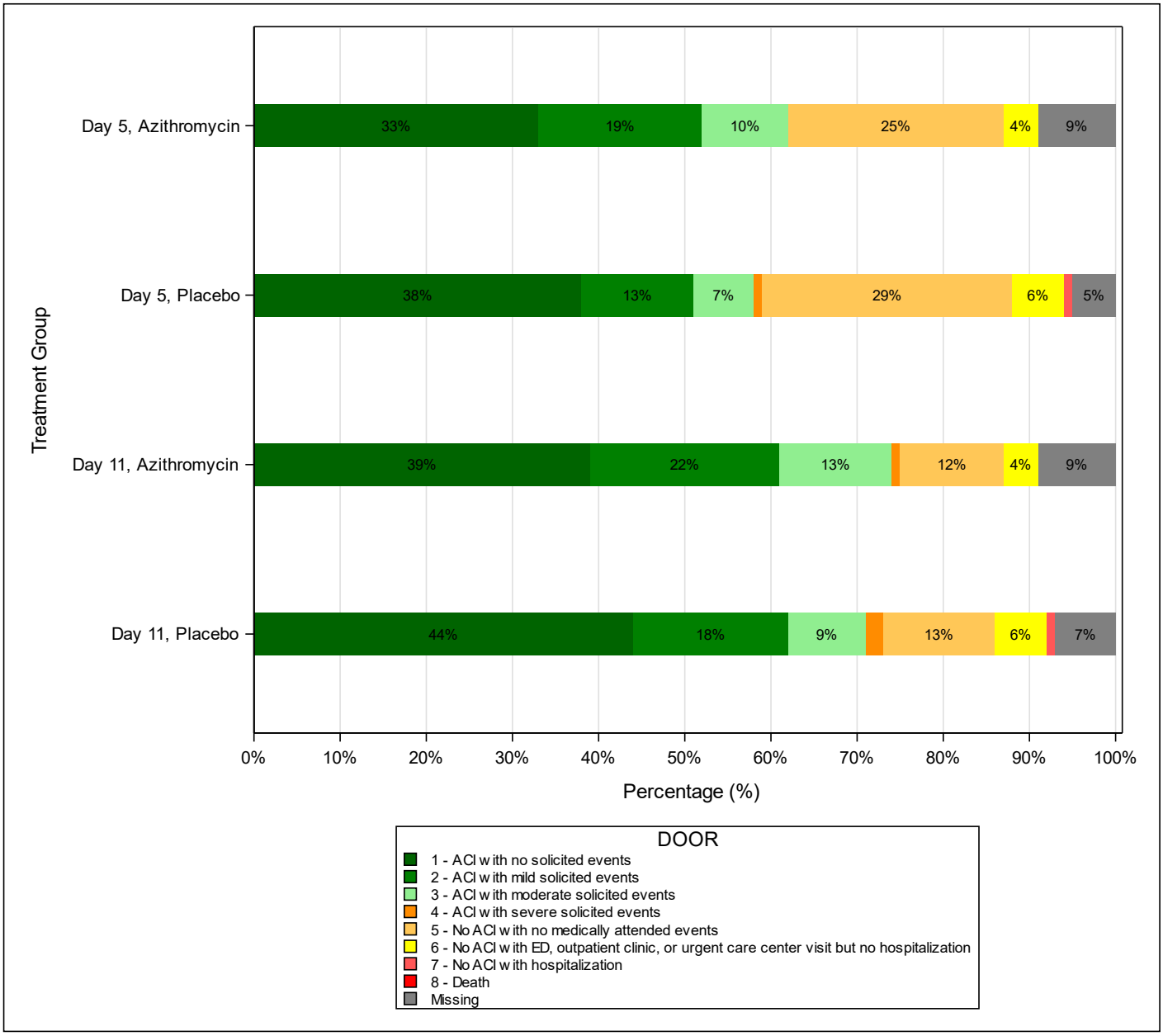
Supplementary Table 1. Desirability of Outcome Ranking (DOOR).

Rank	Adequate Clinical Improvement [a]	Solicited Events [b]
1	Yes	None
2	Yes	Mild (Grade 1)
3	Yes	Moderate (Grade 2)
4	Yes	Severe (Grade 3)
5	No adequate clinical improvement with no medically attended events	None or any grade
6	No adequate clinical improvement with ED, outpatient clinic, or urgent care center visit but no hospitalization	None or any grade
7	No adequate clinical improvement with hospitalization	None or any grade
8	Death (any cause)	--

[a] Adequate clinical improvement was defined as improvement in at least two qualifying symptoms (or one symptom and one vital sign abnormality); no deterioration in any qualifying symptom nor new vital sign abnormality; absence of fever in the 24-hours prior to the Day 5 visit; and no medically attended visits where antibacterial therapy was prescribed for persistent or worsening LRTI.

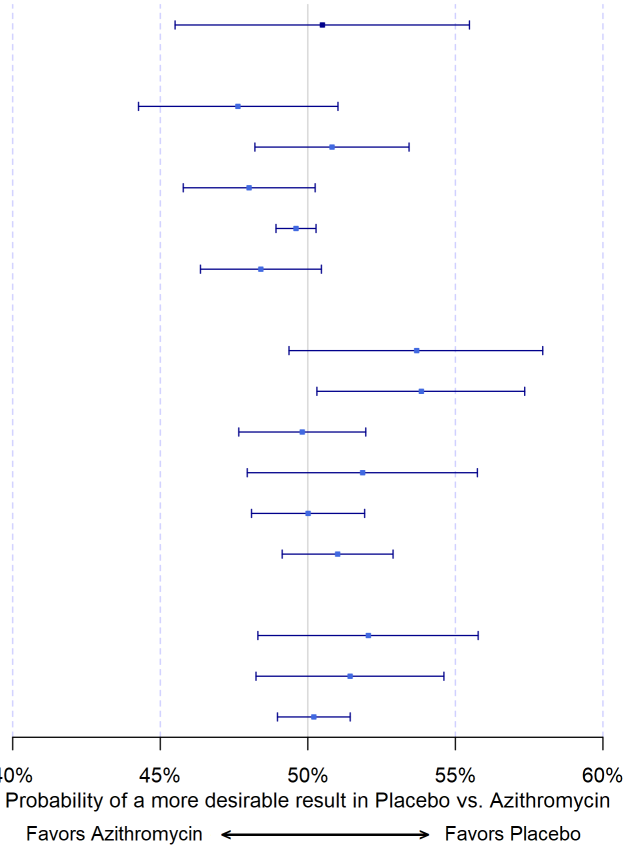
[b] Solicited adverse events included abdominal pain, vomiting, diarrhea, allergic reactions, or mucocutaneous candidiasis, each of which was graded as mild, moderate, or severe.

Supplementary Figure 1. Desirability of Outcome Ranking at Days 5 and 11. The distribution of desirability of outcome rankings is shown for the ITT azithromycin- and placebo-treated groups at Days 5 and 11. Lower numerical values represent better outcomes, factoring in clinical improvement and solicited adverse events. The placebo-treated group had higher probabilities of a better rank at both Days 5 and 11. Solicited events included abdominal pain, vomiting, diarrhea, allergic reactions, or mucocutaneous candidiasis. ACI = Adequate Clinical Improvement. Solicited events include abdominal pain, vomiting, diarrhea, allergic reactions, or mucocutaneous candidiasis.



Supplementary Figure 2. Clinical improvement and solicited events among azithromycin-treated and placebo-treated subjects at Day 11. The desirability of outcome ranking (DOOR) incorporates elements of clinical improvement and solicited adverse events while simultaneously considering the severity of those adverse events. Presented values indicate the probability of a more desirable DOOR when assigned to placebo vs. azithromycin. Probabilities above 50% indicate a more favorable DOOR with placebo treatment. Rather than reporting probabilities of adequate clinical improvement (a study endpoint), we report its absence to align the treatment-dependent directionality show in the figure.

	Azithromycin (N=249) n(%)	Placebo (N=250) n(%)	DOOR probability* (95% CI)
DOOR			**50% (46%, 56%)**
Absence of Clinical Improvement			
Any qualifying event	39(16%)	51(20%)	48% (44%, 51%)
Absence of improvement in at least 2 symptoms or signs	26(10%)	22(9%)	51% (48%, 53%)
Deterloration in any sign or symptom	12(5%)	22(9%)	48% (46%, 50%)
Presence of fever in day preceding or at visit	0(0%)	2(1%)	50% (49%, 50%)
Medically attended visit for persistent or worsening LRTI	10(4%)	18(7%)	48% (46%, 50%)
Solicited Events			
Any qualifying event	111(45%)	93(37%)	54% (49%, 58%)
Abdominal pain	60(24%)	41(16%)	54% (50%, 57%)
Vomiting	15(6%)	16(6%)	50% (48%, 52%)
Diarrhea	72(29%)	63(25%)	52% (48%, 56%)
Allergic reaction	12(5%)	12(5%)	50% (48%, 52%)
Candidiasis	14(6%)	9(4%)	51% (49%, 53%)
Severity of Solicited Events			
Mild	64(26%)	54(22%)	52% (48%, 56%)
Moderate	42(17%)	35(14%)	51% (48%, 55%)
severe	5(2%)	4(2%)	50% (49%, 51%)



Supplementary Table 2. Change in cytokine levels from Day 1 to Day 5 stratified by treatment group or clinical improvement. Results are not shown for IL-1β, IL-2, IL-4, IL-12p70, and IL-13 due to high rates of undetectable levels (68-94% of samples).

Cytokine[a]	Azithromycin (n=172)	Placebo (n=202)	P-value[b]	Clinical Improvement (n=236)	Lack of Clinical Improvement (n=136)	P-value[b]
IL-6 (pg/ml)	-0·9 (-2·5, -0·0)	-0·8 (-2·6, 0·1)	0·458	-0·7 (-2·6, 0·0)	-0·9 (-2·4, 0·0)	0·994
IL-8 (pg/ml)	-1·5 (-3·4, 0·0)	-0·4 (-2·8, 1·9)	0·002	-1·3 (-3·1, 0·7)	-0·5 (-2·4, 1·5)	0·061
IL-10 (pg/ml)	-0·2 (-0·9, -0·0)	-0·3 (-1·3, 0·0)	0·747	-0·3 (-1·0, -0·0)	-0·2 (-1·3, 0·0)	0·498
IFN-γ(pg/ml)	-3·8 (-43·3, -0·2)	-4·6 (-45·2, 0·2)	0·452	-3·6 (-40·1, 0·0)	-4·8 (-45·7, -0·1)	0·397
TNF-α(pg/ml)	-0·3 (-0·7, -0·0)	-0·2 (-0·7, 0·1)	0·086	-0·2 (-0·7, 0·0)	-0·3 (-0·8, 0·0)	0·600

[a] Results are presented as median (IQR).

[b] P-values were calculated using the Wilcoxon rank sum test.

Supplementary Table 3. IL-8 levels at Day 1 and Day 5 stratified by treatment group and clinical improvement.

	Clinical Improvement			Lack of Clinical Improvement		
	Azithromycin (n=109)	**Placebo** (n=127)	**P-value**[a]	**Azithromycin** (n=63)	**Placebo** (n=73)	**P-value**[a]
Day 1, median (IQR)	8·0 (5·8,10·8)	6·6 (5·3,9·8)	0·033	7·6 (5·5,10·1)	7·0 (4·7,12·5)	0·807
Day 5, median (IQR)	6·2 (4·8,8·3)	6·3 (4·9,8·8)	0·732	6·5 (5·1,8·0)	7·2 (4·9,9·7)	0·156
Day 1-Day 5 change, median (IQR)	-1·8 (-4·0,-0·1)	-0·9 (-2·7,1·2)	0·004	-1·1 (-2·3,0·3)	0·1 (-2·8,2·5)	0·099

[a] P-values were calculated using the Wilcoxon rank sum test.

Supplementary Table 4. Concomitant medications by clinical improvement in the according-to-protocol Day 5 analysis population.

	Azithromycin						Placebo						All Subjects						
WHO Drug Code Level 2, Therapeutic Subgroup	**Drug Taken**			**Drug Not Taken**			**Drug Taken**			**Drug Not Taken**			**Drug Taken**			**Drug Not Taken**			**Difference in Proportions[c]**
	N[a]	**Clinical Success n (%)**	**No Clinical Success n (%)**	**N[b]**	**Clinical Success n (%)**	**No Clinical Success n (%)**	**N[a]**	**Clinical Success n (%)**	**No Clinical Success n (%)**	**N[b]**	**Clinical Success n (%)**	**No Clinical Success n (%)**	**N[a]**	**Clinical Success n (%)**	**No Clinical Success n (%)**	**N[b]**	**Clinical Success n (%)**	**No Clinical Success n (%)**	**% (95% CI)**
ANTIHISTAMINES FOR SYSTEMIC USE	9	4 (44)	5 (56)	195	132 (68)	63 (32)	11	7 (64)	4 (36)	210	129 (61)	81 (39)	20	11 (55)	9 (45)	405	261 (64)	144 (36)	-9 (-30·8, 10·4)
ANTIVIRALS FOR SYSTEMIC USE	9	8 (89)	1 (11)	195	128 (66)	67 (34)	10	5 (50)	5 (50)	211	131 (62)	80 (38)	19	13 (68)	6 (32)	406	259 (64)	147 (36)	5 (-18·3, 21·7)
CORTICOSTEROIDS FOR SYSTEMIC USE	25	14 (56)	11 (44)	179	122 (68)	57 (32)	37	24 (65)	13 (35)	184	112 (61)	72 (39)	62	38 (61)	24 (39)	363	234 (64)	129 (36)	-3 (-16·5, 9·1)
COUGH AND COLD PREPARATIONS	53	31 (58)	22 (42)	151	105 (70)	46 (30)	52	32 (62)	20 (38)	169	104 (62)	65 (38)	105	63 (60)	42 (40)	320	209 (65)	111 (35)	-5 (-16·2, 5·1)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	39	26 (67)	13 (33)	165	110 (67)	55 (33)	53	35 (66)	18 (34)	168	101 (60)	67 (40)	92	61 (66)	31 (34)	333	211 (63)	122 (37)	3 (-8·4, 13·3)
NASAL PREPARATIONS	12	8 (67)	4 (33)	192	128 (67)	64 (33)	7	5 (71)	2 (29)	214	131 (61)	83 (39)	19	13 (68)	6 (32)	406	259 (64)	147 (36)	5 (-18·3, 21·7)

[a] N represents the number of subjects in the ATP-5 population for the corresponding treatment group who took the corresponding medication of interest between enrollment and Day 5 visit day and serves as the denominator for percent calculations under 'Drug Taken'.

[b] N represents the number of subjects in the ATP-5 population for the corresponding treatment group who did not take the corresponding medication of interest between enrollment and Day 5 visit day and serves as the denominator for percent calculations under 'Drug Not Taken'.

[c] Difference in proportions of clinical success for drug taken compared to drug not taken groups regardless of treatment group. The 95% CI is calculated using the Miettinen–Nurminen method.

Supplementary Table 5. Concomitant medications by clinical improvement in the according-to-protocol Day 11 analysis population.

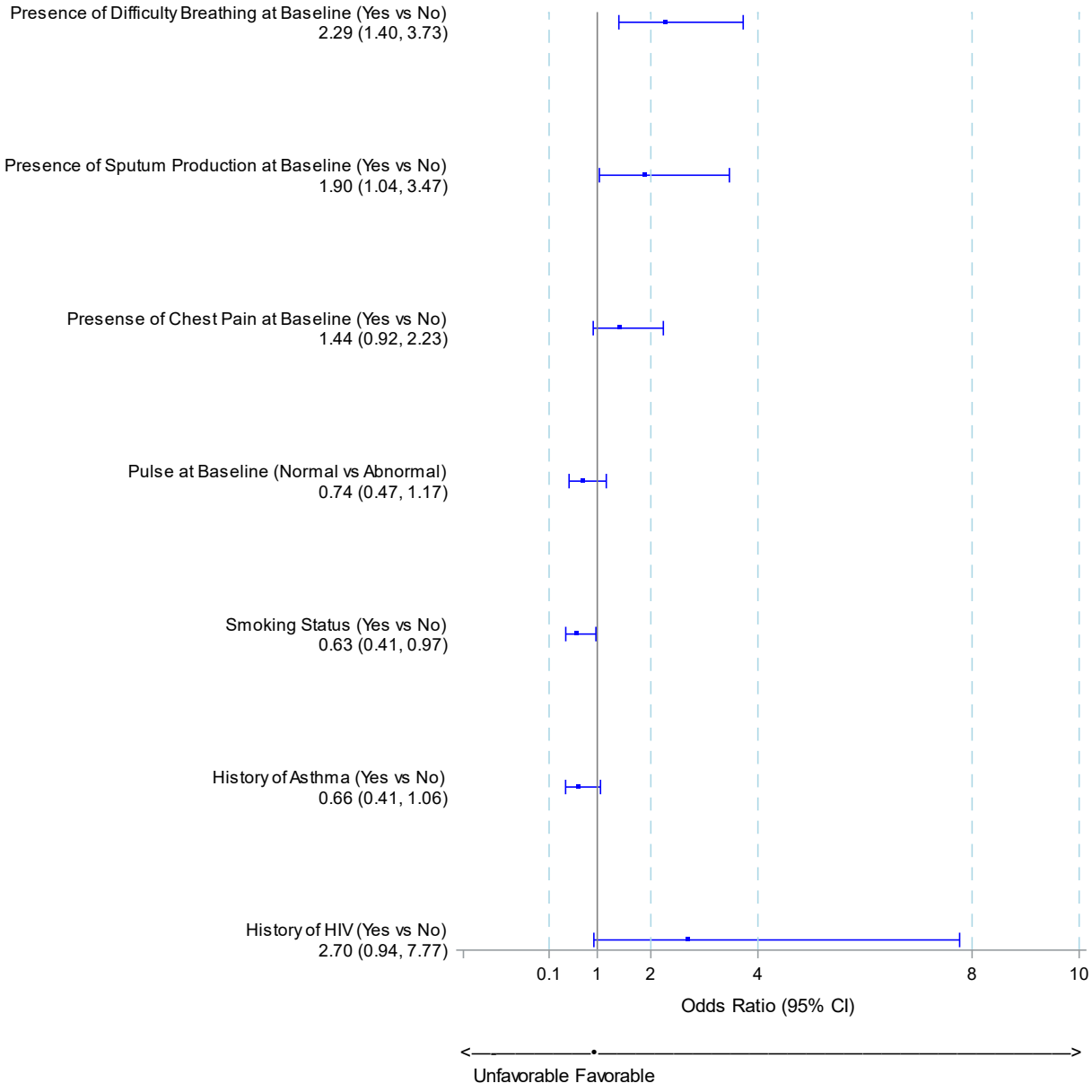
	Azithromycin						Placebo						All Subjects						
WHO Drug Code Level 2, Therapeutic Subgroup	**Drug Taken**			**Drug Not Taken**			**Drug Taken**			**Drug Not Taken**			**Drug Taken**			**Drug Not Taken**			**Difference in Proportions[c]**
	N[a]	**Clinical Success n (%)**	**No Clinical Success n (%)**	**N[b]**	**Clinical Success n (%)**	**No Clinical Success n (%)**	**N[a]**	**Clinical Success n (%)**	**No Clinical Success n (%)**	**N[b]**	**Clinical Success n (%)**	**No Clinical Success n (%)**	**N[a]**	**Clinical Success n (%)**	**No Clinical Success n (%)**	**N[b]**	**Clinical Success n (%)**	**No Clinical Success n (%)**	**% (95% CI)**
ANTIHISTAMINES FOR SYSTEMIC USE	8	6 (75)	2 (25)	203	168 (83)	35 (17)	12	8 (67)	4 (33)	213	169 (79)	44 (21)	20	14 (70)	6 (30)	416	337 (81)	79 (19)	-11 (-33·2, 5·0)
ANTIVIRALS FOR SYSTEMIC USE	11	10 (91)	1 (9)	200	164 (82)	36 (18)	10	7 (70)	3 (30)	215	170 (79)	45 (21)	21	17 (81)	4 (19)	415	334 (80)	81 (20)	0 (-20·8, 12·7)
CORTICOSTEROIDS FOR SYSTEMIC USE	31	24 (77)	7 (23)	180	150 (83)	30 (17)	38	30 (79)	8 (21)	187	147 (79)	40 (21)	69	54 (78)	15 (22)	367	297 (81)	70 (19)	-3 (-14·4, 6·6)
COUGH AND COLD PREPARATIONS	55	46 (84)	9 (16)	156	128 (82)	28 (18)	55	39 (71)	16 (29)	170	138 (81)	32 (19)	110	85 (77)	25 (23)	326	266 (82)	60 (18)	-4 (-13·8, 3·9)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	46	37 (80)	9 (20)	165	137 (83)	28 (17)	58	41 (71)	17 (29)	167	136 (81)	31 (19)	104	78 (75)	26 (25)	332	273 (82)	59 (18)	-7 (-17·1, 1·4)
NASAL PREPARATIONS	11	10 (91)	1 (9)	200	164 (82)	36 (18)	8	5 (63)	3 (38)	217	172 (79)	45 (21)	19	15 (79)	4 (21)	417	336 (81)	81 (19)	-2 (-24·2, 11·7)

[a] N represents the number of subjects in the ATP-11 population for the corresponding treatment group who took the corresponding medication of interest between enrollment and Day 11 visit day and serves as the denominator for percent calculations under 'Drug Taken'.

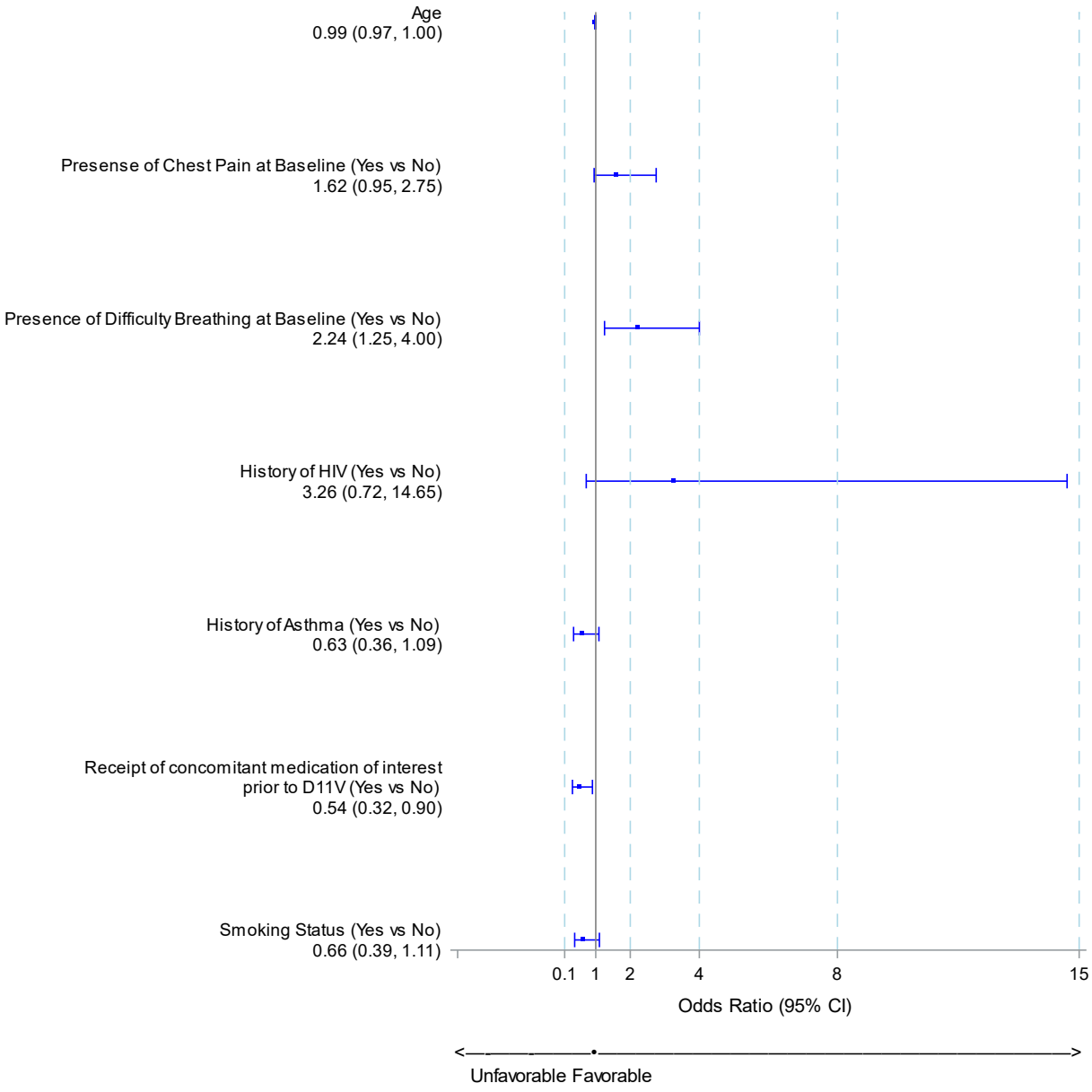
[b] N represents the number of subjects in the ATP-11 population for the corresponding treatment group who did not take the corresponding medication of interest between enrollment and Day 11 visit day and serves as the denominator for percent calculations under 'Drug Not Taken'.

[c] Difference in proportions of clinical success for drug taken compared to drug not taken groups regardless of treatment group. The 95% CI is calculated using the Miettinen–Nurminen method.

Supplementary Figure 3. Logistic regression model of variables associated with clinical improvement at Day 5 without treatment stratification. Each point represents the estimate of the odds ratio from a logistic regression model to determine variables associated with clinical improvement. Variables were selected for the final model using a stepwise model selection approach with a value of 0·2 as the significance level for entry and staying in the model. An odds ratio greater than 1 indicates clinical improvement.

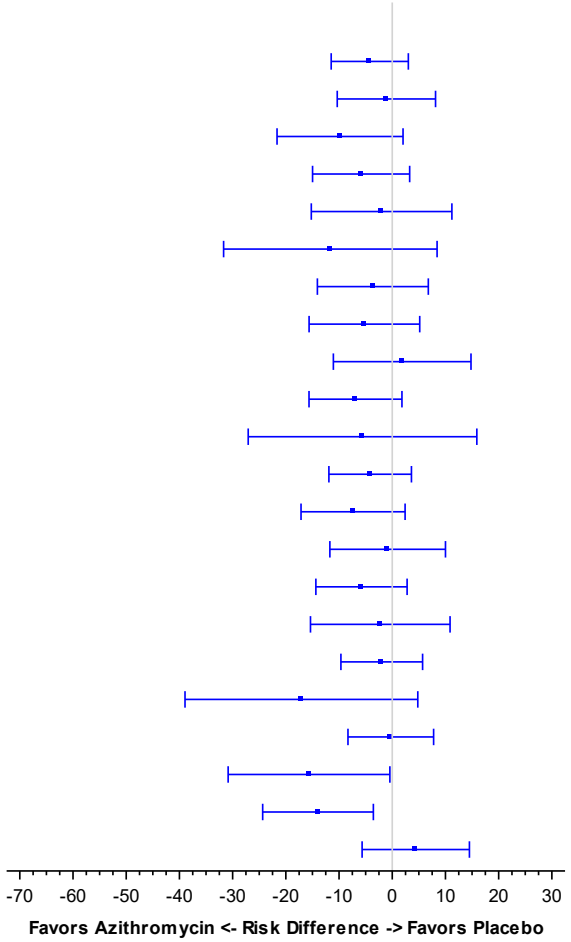


Supplementary Figure 4. Logistic regression model of variables associated with clinical improvement at Day 11 without treatment stratification. Each point represents the estimate of the odds ratio from a logistic regression model to determine variables associated with clinical improvement. Variables were selected for the final model using a stepwise model selection approach with a value of 0·2 as the significance level for entry and staying in the model. An odds ratio greater than 1 indicates clinical improvement.



Supplementary Figure 5. Forest plot of baseline characteristics by clinical improvement in the intent-to-treat Day 11 analysis population. Each point estimate and error bars represent the estimate of the difference in rates of clinical improvement at Day 11 and the associated 95% CI obtained from a linear regression model. A difference in rates greater than zero favors azithromycin. Interaction p-values are obtained from an interaction Type III test where the interaction term between subgroup variable and treatment is being added to the linear regression model.

		Azithromycin (N=249) n (%)	Placebo (N=250) n (%)	Risk Difference % (95% CI)	Interaction P-Value
All Subjects	-	187 (80)	184 (76)	-4 (-11, 3)	-
Sex	Male	122 (78)	111 (77)	-1 (-10, 8)	0.487
	Female	65 (85)	73 (76)	-10 (-22, 2)	
Race	Black or African American	119 (80)	108 (74)	-6 (-15, 3)	0.305
	White	60 (79)	64 (77)	-2 (-15, 11)	
	Other	8 (96)	12 (85)	-12 (-32, 8)	
Smoking Status	Yes	96 (77)	97 (73)	-4 (-14, 7)	0.407
	No	88 (85)	81 (79)	-5 (-16, 5)	
Asthma	Yes	55 (82)	66 (84)	2 (-11, 15)	0.503
	No	132 (79)	118 (73)	-7 (-16, 2)	
COPD	Yes	18 (81)	27 (75)	-6 (-27, 16)	0.931
	No	169 (80)	157 (76)	-4 (-12, 4)	
Viral infection	Yes	99 (83)	99 (76)	-7 (-17, 2)	0.575
	No	88 (78)	85 (77)	-1 (-12, 10)	
Chest Pain at Baseline	Yes	121 (84)	123 (78)	-6 (-14, 3)	0.135
	No	66 (76)	61 (73)	-2 (-15, 11)	
Sputum Production at Baseline	Yes	165 (80)	159 (78)	-2 (-10, 6)	0.192
	No	22 (81)	25 (64)	-17 (-39, 5)	
Difficulty Breathing at Baseline	Yes	136 (83)	143 (83)	0 (-8, 8)	0.007
	No	51 (72)	41 (57)	-16 (-31, 0)	
Fever at Baseline	Yes	93 (85)	82 (71)	-14 (-24, -4)	0.045
	No	94 (76)	102 (80)	4 (-6, 15)	



Secondary Outcome Measures

1. All antibiotic use from Day 1 through Day 11 and from Day 1 through Day 28 in each treatment group

2. The proportion of subjects with one or more unplanned return visits to a physician's office or urgent care for persistent or worsening LRTI from Day 1 through Day 11 and from Day 1 through Day 28 in each treatment group

3. The proportion of subjects with one or more emergency department visits for persistent or worsening from Day 1 through Day 11 and from Day 1 through Day 28 in each treatment group

4. The proportion of subjects with one or more hospitalizations for persistent or worsening LRTI (if not hospitalized at the enrollment visit) from Day 1 through Day 11 and from Day 1 through Day 28 in each treatment group

5. The proportion of subjects exhibiting improvement in at least one presenting symptom at Day 11 and at Day 28 in each treatment group

6. Outcome assessed employing a superiority analysis using the "Response Adjusted for Days of Antibiotic Risk (RADAR)" approach.

- The endpoint/outcome measure is the composite overall Desirability Of Outcome Ranking (DOOR) at Outcome Assessment on Day 5
- DOOR is defined as follows:
    - Each subject is evaluated according to the ordinal clinical outcome (See Table below)
    - DOOR is then assigned according to two rules:
        - When comparing two subjects with different ordinal clinical outcomes, the subject with a better clinical outcome receives a higher rank.
        - When comparing two subjects with the same ordinal clinical outcomes, the subject with fewer days of antibiotic use receives a higher rank.

Ordinal Clinical Outcomes Assessed at Day 5

	Adequate Clinical Improvement* (Assessed at Outcome Assessment Day 5)	Solicited Events** (Assessed through Outcome Assessment Day 5)
1	Yes	None
2	Yes	Mild (Grade 1)
3	Yes	Moderate (Grade 2)
4	Yes	Severe (Grade 3)
5	No adequate clinical improvement with no medically attended events	None or any grade
6	No adequate clinical improvement with ED, outpatient clinic, or urgent care center visit but no hospitalization	None or any grade
7	No adequate clinical improvement with hospitalization	None or any grade
8	Death (any cause)	--

* Clinical improvement as defined for the primary outcome.
** Solicited events are defined below.

Solicited Adverse Events for RADAR-DOOR ranking

	Mild	Moderate	Severe
Abdominal pain	Mild or intermittent and does not interfere with daily activity	Moderate or persistent and interferes with daily activity but did not necessitate a medical visit or absenteeism	Prevents daily activity and resulted in medical visit or absenteeism
Vomiting	1 episode/day	2-3 episodes/day	≥4 episodes/day
Diarrhea	Looser than normal stools occurring 3-6 times/day	Looser than normal stools >6 times/day	Bloody diarrhea or diarrhea that requires clinical evaluation, laboratory testing, or hospitalization
Allergic reaction	New localized rash or	New diffuse rash	New rash requiring

	itching without rash	covering multiple areas of the body	clinical visit
Candidiasis	Mild mucocutaneous candidiasis, with no treatment	Moderate mucocutaneous candidiasis, requiring topical or other over-the-counter treatment	Severe mucocutaneous candidiasis; requires urgent clinical evaluation, intravenous treatment, or hospitalization

7. Proportion of subjects reporting solicited adverse events from Day 1 to Day 5 in each treatment group

8. Proportion of subjects reporting one or more hospitalization or visits to an ED, outpatient clinic, or urgent care center (after randomization) for worsening or persistent LRTI from Day 1 through Day 5 in each treatment group

9. The proportion of subjects exhibiting improvement in at least one presenting sign or symptom at Day 5 in each treatment group

10. The proportion of subjects exhibiting worsening or deterioration in at least one or more symptoms at Day 5 in each treatment group. The proportion of subjects with a new occurrence of a vital sign abnormality at Day 5 in each treatment group.