

Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1: Other Reasons for Refusing Study Participation

Reason	N
Unable to consent in English	4
No medical insurance	2
Too ill to participate	1
Mistrustful of study sponsor	1
Study is too much work	1
Unable to reach	1
Did not want single dose	1
Did not want an antibiotic	1
Able to get Z-pak from physician	1
Did not want azithromycin	1

eTable 2: Baseline Characteristics, Medications, and Symptoms Among Those Who Were Retained at the Day 14 Timepoint

	Azithromycin N=131	Placebo N=70
Age, years, median (IQR)	42 (36 to 50)	44 (34 to 51)
Gender identity		
Female, N (%)	90 (69%)	40 (57%)
Male, N (%)	40 (31%)	30 (43%)
Geographic region ^a		
West	63 (48%)	31 (44%)
Southeast	25 (19%)	10 (14%)
Southwest	17 (13%)	11 (16%)
Midwest	18 (14%)	13 (19%)
Northeast	8 (6%)	5 (7%)
Race/ethnicity (N=198) ^b		
Non-Hispanic White	74 (57%)	40 (57%)
Latinx/Hispanic	36 (28%)	24 (34%)
Non-Hispanic Black	7 (5%)	0 (0%)
Non-Hispanic Asian	5 (4%)	3 (4%)
Mixed Race	3 (2%)	2 (3%)
Non-Hispanic Middle Eastern/Arab	2 (2%)	1 (1%)
Prefer not to answer	1 (1%)	0 (0%)
Alcohol consumption >3x/week ^c , N (%)	17 (13%)	7 (10%)
Current cigarette smoker, N (%)	10 (8%)	3 (4%)
Current marijuana user, N (%)	7 (5%)	4 (6%)
Current e-cigarette/vaping, N (%)	6 (5%)	1 (1%)
Current cigar use, N (%)	1 (1%)	1 (1%)
Comorbidities ^d		
Asthma	17 (13%)	8 (11%)
Hypertension	14 (11%)	11 (16%)
Diabetes	4 (3%)	4 (6%)
Chronic obstructive pulmonary disease	2 (2%)	0 (0%)
Chronic kidney disease	0 (0%)	1 (1%)
Cancer	1 (1%)	0 (0%)
Stroke	0 (0%)	1 (1%)
Recent macrolide use (<30 days), N (%)	14 (11%)	7 (10%)
Recent hydroxychloroquine use (<7 days), N (%)	1 (1%)	0 (0%)
Current medications ^e		
ACE/ARB inhibitor	13 (10%)	10 (14%)
Metformin	3 (2%)	2 (3%)
Omeprazole	1 (1%)	0 (0%)
Tacrolimus	1 (1%)	0 (0%)
Current vitamin/supplement use ^f		
Vitamin D	49 (37%)	27 (39%)
Vitamin C	47 (36%)	24 (34%)
Multivitamin	40 (31%)	20 (29%)
Zinc	36 (28%)	16 (23%)
Omega-3 fatty acid	11 (8%)	5 (7%)
Self-reported symptoms		
Multiple symptoms	116 (89%)	64 (91%)

Cough	93 (71%)	48 (69%)
Fatigue	78 (60%)	44 (63%)
Fever	63 (48%)	31 (44%)
Myalgia	62 (47%)	33 (47%)
Anosmia	62 (47%)	29 (41%)
Sore throat	55 (42%)	30 (43%)
Diarrhea	34 (26%)	18 (26%)
Shortness of breath	31 (24%)	12 (17%)
Dizziness	32 (24%)	13 (19%)
Abdominal pain	18 (14%)	10 (14%)
None	10 (8%)	4 (6%)
Conjunctivitis	7 (5%)	2 (3%)
Duration of symptoms prior to test, median (IQR)	3 (2 to 4)	3 (2 to 4)
Days between positive test and enrollment, median (IQR)	3 (2 to 5)	3 (1 to 4)

^aWest: Colorado, Montana, Washington, Utah, Nevada, California; Southwest: Texas, Oklahoma, New Mexico, Arizona; Midwest: Ohio, Indiana, Michigan, Illinois, Missouri, Wisconsin, Minnesota, Iowa, Kansas, Nebraska, South Dakota; Southeast: Virginia, Tennessee, North Carolina, South Carolina, Georgia, Alabama, Arkansas, Louisiana, Florida; Northeast: Connecticut, New York, Pennsylvania, New Jersey; states divided into regions based on geographic and cultural similarities; ^bRace/ethnicity were determined via self-report and are reported for all participants who reported race/ethnicity data; ^cAlcohol consumption more than 3 times per week, regardless of number of drinks; ^dCo-morbidities by participant self-report; ^eCurrent medications per participant self-report; participants were given a list of medications that were thought to be associated with COVID-19 progression at the time of study design (March 2020) and asked to check any that they were currently taking; ^fCurrent supplement use by participant self-report; participants were given a list of vitamins and supplements thought to be associated with COVID-19 progression at the time of study design (March 2020) and asked to check any they were currently taking.

eTable 3: Baseline Characteristics, Medications, and Symptoms Among Those Who Were Not Retained at the Day 14 Timepoint

	Azithromycin N=40	Placebo N=22
Age, years, median (IQR)	42 (32 to 48)	44 (41 to 51)
Gender identity		
Female, N (%)	27 (68%)	17 (77%)
Male, N (%)	11 (28%)	5 (23%)
Geographic region ^a		
West	16 (40%)	9 (41%)
Southeast	13 (33%)	4 (18%)
Southwest	7 (18%)	5 (23%)
Midwest	3 (8%)	3 (14%)
Northeast	1 (3%)	1 (5%)
Race/ethnicity (N=61) ^b		
Non-Hispanic White	20 (50%)	16 (73%)
Latinx/Hispanic	13 (33%)	3 (14%)
Non-Hispanic Black	4 (10%)	1 (5%)
Non-Hispanic Asian	1 (3%)	0 (0%)
Mixed Race	1 (3%)	1 (5%)
Non-Hispanic Middle Eastern/Arab	0 (0%)	0 (0%)
Prefer not to answer	0 (0%)	0 (0%)
Alcohol consumption >3x/week ^c , N (%)	6 (15%)	2 (9%)
Current cigarette smoker, N (%)	3 (8%)	2 (9%)
Current marijuana user, N (%)	2 (5%)	2 (9%)
Current e-cigarette/vaping, N (%)	2 (5%)	1 (5%)
Current cigar use, N (%)	0 (0%)	0 (0%)
Comorbidities ^d		
Asthma	4 (10%)	3 (14%)
Hypertension	6 (15%)	1 (5%)
Diabetes	1 (3%)	1 (5%)
Chronic obstructive pulmonary disease	2 (5%)	0 (0%)
Chronic kidney disease	1 (3%)	0 (0%)
Cancer	0 (0%)	0 (0%)
Stroke	1 (3%)	0 (0%)
Recent macrolide use (<30 days), N (%)	8 (20%)	4 (18%)
Recent hydroxychloroquine use (<7 days), N (%)	0 (0%)	0 (0%)
Current medications ^e		
ACE/ARB inhibitor	2 (5%)	4 (18%)
Metformin	1 (3%)	1 (3%)
Omeprazole	0 (0%)	1 (5%)
Tacrolimus	0 (0%)	0 (0%)
Current vitamin/supplement use ^f		
Vitamin D	15 (38%)	10 (46%)
Vitamin C	14 (35%)	9 (41%)
Multivitamin	12 (30%)	7 (32%)
Zinc	13 (33%)	4 (18%)
Omega-3 fatty acid	3 (8%)	1 (5%)
Self-reported symptoms		
Multiple symptoms	39 (90%)	18 (82%)

Cough	18 (45%)	13 (59%)
Fatigue	29 (73%)	11 (50%)
Fever	24 (60%)	9 (41%)
Myalgia	20 (50%)	7 (32%)
Anosmia	18 (45%)	10 (46%)
Sore throat	16 (40%)	7 (32%)
Diarrhea	11 (28%)	2 (9%)
Shortness of breath	14 (35%)	5 (23%)
Dizziness	7 (18%)	2 (9%)
Abdominal pain	11 (28%)	2 (9%)
None	2 (5%)	2 (9%)
Conjunctivitis	1 (3%)	0 (0%)
Duration of symptoms prior to test, median (IQR)	3 (2 to 5)	3 (2.75 to 4)
Days between positive test and enrollment, median (IQR)	2.5 (1 to 5)	1.5 (1 to 3)

^aWest: Colorado, Montana, Washington, Utah, Nevada, California; Southwest: Texas, Oklahoma, New Mexico, Arizona; Midwest: Ohio, Indiana, Michigan, Illinois, Missouri, Wisconsin, Minnesota, Iowa, Kansas, Nebraska, South Dakota; Southeast: Virginia, Tennessee, North Carolina, South Carolina, Georgia, Alabama, Arkansas, Louisiana, Florida; Northeast: Connecticut, New York, Pennsylvania, New Jersey; states divided into regions based on geographic and cultural similarities; ^bRace/ethnicity were determined via self-report and are reported for all participants who reported race/ethnicity data; ^cAlcohol consumption more than 3 times per week, regardless of number of drinks; ^dCo-morbidities by participant self-report; ^eCurrent medications per participant self-report; participants were given a list of medications that were thought to be associated with COVID-19 progression at the time of study design (March 2020) and asked to check any that they were currently taking; ^fCurrent supplement use by participant self-report; participants were given a list of vitamins and supplements thought to be associated with COVID-19 progression at the time of study design (March 2020) and asked to check any they were currently taking.

eTable 4: Baseline Characteristics, Medications, and Symptoms Among Those Who Were and Were Not Retained at the 14-Day Timepoint

	Missing (N=62)	Present (N=201)
Randomized treatment group		
Azithromycin	40 (65%)	131 (65%)
Placebo	22 (36%)	70 (35%)
Age, years, median (IQR)	43 (35 to 50)	43 (35 to 50)
Gender identity		
Female, N (%)	44 (71%)	130 (65%)
Male, N (%)	16 (26%)	70 (35%)
Geographic region ^a		
West	25 (40%)	94 (47%)
Southeast	17 (27%)	35 (17%)
Southwest	12 (19%)	28 (14%)
Midwest	6 (10%)	31 (15%)
Northeast	2 (3%)	13 (7%)
Race/ethnicity (N=259) ^b		
Non-Hispanic White	36 (58%)	114 (57%)
Latinx/Hispanic	16 (26%)	60 (30%)
Non-Hispanic Black	5 (8%)	7 (4%)
Non-Hispanic Asian	1 (2%)	8 (4%)
Mixed Race	2 (3%)	5 (3%)
Non-Hispanic Middle Eastern/Arab	0 (0%)	3 (2%)
Prefer not to answer	0 (0%)	1 (1%)
Alcohol consumption >3x/week ^c , N (%)	8 (13%)	24 (12%)
Current cigarette smoker, N (%)	5 (8%)	13 (7%)
Current marijuana user, N (%)	4 (7%)	11 (6%)
Current e-cigarette/vaping, N (%)	3 (5%)	7 (4%)
Current cigar use, N (%)	0 (0%)	2 (1%)
Comorbidities ^d		
Asthma	7 (11%)	25 (12%)
Hypertension	7 (11%)	25 (12%)
Diabetes	2 (3%)	8 (4%)
Chronic obstructive pulmonary disease	2 (3%)	2 (1%)
Chronic kidney disease	1 (2%)	1 (1%)
Cancer	0 (0%)	1 (1%)
Stroke	1 (2%)	1 (1%)
Recent macrolide use (<30 days), N (%)	12 (19%)	21 (10%)
Recent hydroxychloroquine use (<7 days), N (%)	0 (0%)	1 (1%)
Current medications ^e		
ACE/ARB inhibitor	6 (10%)	23 (11%)
Metformin	2 (3%)	5 (3%)
Omeprazole	1 (2%)	1 (1%)
Tacrolimus	0 (0%)	1 (1%)
Current vitamin/supplement use ^f		
Vitamin D	25 (40%)	76 (38%)
Vitamin C	23 (37%)	71 (35%)
Multivitamin	19 (31%)	60 (30%)

Zinc	17 (27%)	52 (26%)
Omega-3 fatty acid	4 (7%)	16 (8%)
Self-reported symptoms		
Multiple symptoms	54 (87%)	180 (90%)
Cough	31 (50%)	141 (70%)
Fatigue	40 (65%)	122 (61%)
Fever	33 (53%)	94 (47%)
Myalgia	27 (44%)	95 (47%)
Anosmia	28 (45%)	91 (45%)
Sore throat	23 (37%)	85 (42%)
Diarrhea	13 (21%)	52 (26%)
Shortness of breath	19 (31%)	43 (21%)
Dizziness	9 (15%)	45 (22%)
Abdominal pain	13 (21%)	28 (14%)
None	4 (7%)	14 (7%)
Conjunctivitis	1 (2%)	9 (5%)
Duration of symptoms prior to test, median (IQR)	3 (2 to 4)	3 (2 to 4)
Days between positive test and enrollment, median (IQR)	2 (1 to 4)	3 (1 to 5)

^aWest: Colorado, Montana, Washington, Utah, Nevada, California; Southwest: Texas, Oklahoma, New Mexico, Arizona; Midwest: Ohio, Indiana, Michigan, Illinois, Missouri, Wisconsin, Minnesota, Iowa, Kansas, Nebraska, South Dakota; Southeast: Virginia, Tennessee, North Carolina, South Carolina, Georgia, Alabama, Arkansas, Louisiana, Florida; Northeast: Connecticut, New York, Pennsylvania, New Jersey; states divided into regions based on geographic and cultural similarities; ^bRace/ethnicity were determined via self-report and are reported for all participants who reported race/ethnicity data; ^cAlcohol consumption more than 3 times per week, regardless of number of drinks; ^dCo-morbidities by participant self-report; ^eCurrent medications per participant self-report; participants were given a list of medications that were thought to be associated with COVID-19 progression at the time of study design (March 2020) and asked to check any that they were currently taking; ^fCurrent supplement use by participant self-report; participants were given a list of vitamins and supplements thought to be associated with COVID-19 progression at the time of study design (March 2020) and asked to check any they were currently taking.

eTable 5: Baseline Characteristics, Medications, and Symptoms Among Those Who Did and Did Not Report Taking Study Medication

This table excludes participants with missing treatment adherence information (N=47).

	Did Not Take Medication (N=22)	Took Medication (N=194)
Randomized treatment group		
Azithromycin	16 (73%)	129 (67%)
Placebo	6 (27%)	65 (33%)
Age, years, median (IQR)	44.5 (36 to 50)	43 (34 to 50)
Gender identity		
Female, N (%)	20 (91%)	124 (64%)
Male, N (%)	2 (9%)	68 (35%)
Geographic region ^a		
West	8 (36%)	89 (46%)
Southeast	5 (23%)	12 (6%)
Southwest	6 (27%)	27 (14%)
Midwest	1 (5%)	31 (16%)
Northeast	2 (9%)	12 (6%)
Race/ethnicity (N=259) ^b		
Non-Hispanic White	12 (55%)	114 (59%)
Latinx/Hispanic	10 (46%)	50 (26%)
Non-Hispanic Black	0 (0%)	9 (5%)
Non-Hispanic Asian	0 (0%)	8 (4.1%)
Mixed Race	0 (0%)	6 (3%)
Non-Hispanic Middle Eastern/Arab	0 (0%)	2 (1%)
Prefer not to answer	0 (0%)	1 (1%)
Alcohol consumption >3x/week ^c , N (%)	0 (0%)	27 (14%)
Current cigarette smoker, N (%)	3 (14%)	13 (7%)
Current marijuana user, N (%)	1 (5%)	13 (7%)
Current e-cigarette/vaping, N (%)	1 (5%)	8 (4%)
Current cigar use, N (%)	0 (0%)	1 (1%)
Comorbidities ^d		
Asthma	3 (14%)	22 (11%)
Hypertension	1 (5%)	24 (12%)
Diabetes	1 (5%)	7 (4%)
Chronic obstructive pulmonary disease	0 (0%)	3 (2%)
Chronic kidney disease	0 (0%)	1 (1%)
Cancer	0 (0%)	1 (1%)
Stroke	0 (0%)	1 (1%)
Recent macrolide use (<30 days), N (%)	7 (32%)	19 (10%)
Recent hydroxychloroquine use (<7 days), N (%)	0 (0%)	1 (1%)
Current medications ^e		
ACE/ARB inhibitor	1 (5%)	21 (11%)
Metformin	0 (0%)	6 (3%)
Omeprazole	0 (0%)	1 (1%)
Tacrolimus	0 (0%)	1 (1%)

Current vitamin/supplement use ^f		
Vitamin D	9 (41%)	72 (37%)
Vitamin C	10 (46%)	66 (34%)
Multivitamin	11 (50%)	57 (29%)
Zinc	4 (18%)	52 (27%)
Omega-3 fatty acid	1 (5%)	16 (8%)
Self-reported symptoms		
Multiple symptoms	20 (91%)	172 (89%)
Cough	16 (73%)	129 (67%)
Fatigue	14 (64%)	120 (62%)
Fever	12 (55%)	90 (46%)
Myalgia	16 (73%)	84 (43%)
Anosmia	11 (50%)	90 (46%)
Sore throat	5 (23%)	89 (46%)
Diarrhea	6 (27%)	129 (67%)
Shortness of breath	6 (27%)	40 (21%)
Dizziness	2 (9%)	43 (22%)
Abdominal pain	3 (14%)	27 (14%)
None	1 (5%)	15 (8%)
Conjunctivitis	0 (0%)	10 (5%)
Duration of symptoms prior to test, median (IQR)	3 (2 to 4)	3 (2 to 4)
Days between positive test and enrollment, median (IQR)	3 (1.25 to 4)	3 (1 to 5)

^aWest: Colorado, Montana, Washington, Utah, Nevada, California; Southwest: Texas, Oklahoma, New Mexico, Arizona; Midwest: Ohio, Indiana, Michigan, Illinois, Missouri, Wisconsin, Minnesota, Iowa, Kansas, Nebraska, South Dakota; Southeast: Virginia, Tennessee, North Carolina, South Carolina, Georgia, Alabama, Arkansas, Louisiana, Florida; Northeast: Connecticut, New York, Pennsylvania, New Jersey; states divided into regions based on geographic and cultural similarities; ^bRace/ethnicity were determined via self-report and are reported for all participants who reported race/ethnicity data; ^cAlcohol consumption more than 3 times per week, regardless of number of drinks; ^dCo-morbidities by participant self-report; ^eCurrent medications per participant self-report; participants were given a list of medications that were thought to be associated with COVID-19 progression at the time of study design (March 2020) and asked to check any that they were currently taking; ^fCurrent supplement use by participant self-report; participants were given a list of vitamins and supplements thought to be associated with COVID-19 progression at the time of study design (March 2020) and asked to check any they were currently taking.

eTable 6: Proportion of Participants Reporting Being Symptom Free at Day 14 by Randomized Treatment Group, Unadjusted and Accounting for Missing Outcome Data

Outcome	Azithromycin			Placebo			Prevalence Difference (95% CI)	Prevalence Ratio (95% CI)
	N	n	(%)	N	n	(%)		
Unadjusted	131	66	(50%)	70	35	(50%)	0.00 (-0.14, 0.15)	1.01 (0.76, 1.39)
IPCW-adjusted ^a							0.00 (-0.14, 0.15)	1.00 (0.75, 1.35)
MNAR pattern mixture model analysis ^b								
OR associated with missingness: 0.25							0.01 (-0.14, 0.15)	1.02 (0.74, 1.43)
OR associated with missingness: 0.50							0.00 (-0.13, 0.15)	1.01 (0.76, 1.36)
OR associated with missingness: 0.80							-0.00 (-0.16, 0.15)	1.00 (0.72, 1.38)
OR associated with missingness: 1.00							0.00 (-0.15, 0.15)	1.00 (0.74, 1.40)
OR associated with missingness: 1.25							-0.00 (-0.16, 0.14)	1.00 (0.74, 1.34)
OR associated with missingness: 2.00							-0.00 (-0.15, 0.15)	1.00 (0.76, 1.34)
OR associated with missingness: 4.00							-0.01 (-0.15, 0.15)	0.99 (0.77, 1.31)

N: number measured; n: number symptom-free at day 14; ^aIPCW: inverse probability of censoring weighted estimate obtained through targeted maximum likelihood estimation, weighted by the inverse probability of being observed (thus upweighting participants least likely to be observed). IPCW weights were modeled as a function of covariates associated with the outcome: age, gender, alcohol use, marijuana use, and baseline symptoms (fever, cough, sore throat, diarrhea, abdominal pain, shortness of breath, myalgia, fatigue, dizziness). ^bMNAR: missing not at random analysis, in which the outcomes for missing patients were imputed as a function of covariates used in the IPCW analysis, plus assumed systematic differences between missing and non-missing patients in their outcome probability measured using an odds ratio (OR). Final marginal differences estimated assuming a mixture of outcomes among missing and non-missing patients.