

Optimal symptom combinations to aid COVID-19 case identification: analysis from a community-based, prospective, observational cohort

Running title: Optimal symptom combinations for COVID-19

M Antonelli PhD¹, J Capdevila PhD², A Chaudhari MD³, J Granerod PhD³, LS Canas PhD¹, MS Graham PhD¹, K Klaser MSc¹, M Modat PhD¹, E Molteni PhD¹, B Murray MSc¹, CH Sudre PhD^{4,1}, R Davies MA², A May MA², LH Nguyen MD^{5,6}, DA Drew PhD^{5,6}, A Joshi PhD^{5,6}, AT Chan MD^{5,6}, JP Cramer MD³, Professor T Spector⁷, J Wolf MA², Professor S Ourselin¹, CJ Steves PhD^{7*}, AE Loeliger MD³

¹School of Biomedical Engineering & Imaging Sciences, King's College London, London, UK

²Zoe Global, London, UK

³Coalition for Epidemic Preparedness Innovations, London, UK

⁴MRC Unit for Lifelong Health and Ageing at UCL/Centre for Medical Image Computing, Department of Computer Science, UCL, London, UK

⁵Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.

⁶Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.

⁷Department of Twin Research and Genetic Epidemiology, King's College London, London, UK.

Highlights

- Widely recommended symptoms identified only ~70% COVID-19 cases
- Additional symptoms increased case finding to > 90% but tests needed doubled
- Optimal symptom combinations maximise case capture considering available resources
- Implications for COVID-19 vaccine efficacy trials and wider public health

Abstract

Objectives: Diagnostic work-up following any COVID-19 associated symptom will lead to extensive testing, potentially overwhelming laboratory capacity whilst primarily yielding negative results. We aimed to identify optimal symptom combinations to capture most cases using fewer tests with implications for COVID-19 vaccine developers across different resource settings and public health.

Methods: UK and US users of the COVID-19 Symptom Study app who reported new-onset symptoms and an RT-PCR test within seven days of symptom onset were included. Sensitivity, specificity, and number of RT-PCR tests needed to identify one case (test per case [TPC]) were calculated for different symptom combinations. A multi-objective evolutionary algorithm was applied to generate combinations with optimal trade-offs between sensitivity and specificity.

Findings: UK and US cohorts included 122,305 (1,202 positives) and 3,162 (79 positive) individuals. Within three days of symptom onset, the COVID-19 specific symptom combination (cough, dyspnoea, fever, anosmia/ageusia) identified 69% of cases requiring 47 TPC. The combination with highest sensitivity (fatigue, anosmia/ageusia, cough, diarrhoea, headache, sore throat) identified 96% cases requiring 96 TPC.

Interpretation: We confirmed the significance of COVID-19 specific symptoms for triggering RT-PCR and identified additional symptom combinations with optimal trade-offs between sensitivity and specificity that maximize case capture given different resource settings.

Introduction

Safe and effective vaccines represent the most promising intervention to prevent morbidity and mortality during the coronavirus disease (COVID)-19 pandemic.^{1,2} Positive results have recently emerged from three ongoing vaccine efficacy trials of COVID-19 vaccines.³⁻⁵ However, further vaccines are required to meet global demand, and vaccines currently in early development may result in better tolerability profiles, scalability, impact on viral shedding, and may be suitable to specific population subgroups. Thus, further important COVID-19 vaccine efficacy trials are predicted to start soon. In a clinical trial, diagnostic testing of suspected cases (e.g., reverse transcription polymerase chain reaction [RT-PCR] for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) could be triggered by the presence of any COVID-19 associated symptom. A household survey in the United Kingdom (UK) showed that fever, cough, anosmia, and ageusia were present on the day of testing in only 60% of symptomatic, RT-PCR positive individuals, implying that other less specific signs/symptoms associated with COVID-19 occur in a substantial number of patients.⁶ The signs/symptoms associated with COVID-19 are extensive and overlap with those of other common viral infections.^{7,8} Thus, diagnostic work-up following any COVID-19 associated symptom may lead to indiscriminate testing and potentially overwhelm laboratory capacity whilst primarily yielding negative results.

Identification of an efficient symptom combination to trigger diagnostic work-up that will capture the majority of COVID-19 cases using the lowest possible number of tests would enable optimum use of laboratory and financial resources in future vaccine efficacy trials. This would also be of wider benefit in public health settings for the early detection of symptomatic SARS-CoV-2 infection. Such data are scant and the triggering symptoms vary between publicly available vaccine efficacy trial protocols.⁹⁻¹⁵

We simulate COVID-19 case finding in a trial population using a community-based, prospective, observational cohort study. Data from UK COVID Symptom Study app¹⁶ users were used to quantify how much individual COVID-19 symptoms contribute to COVID-19 case finding and to generate symptom combinations with optimal trade-offs between sensitivity and specificity that maximise the capture of RT-PCR positive cases given different laboratory capacities. The findings were replicated in a dataset of COVID Symptom Study app users in the United States (US).

Material

Study design and data source

A community-based cohort study was carried out using data from the COVID Symptom Study app, a free smartphone app launched at the end of March 2020 and developed by Zoe Global (London, UK) in collaboration with King's College London (London, UK) and Massachusetts General Hospital (Boston, MA, USA).¹⁶ Users from UK and US report baseline demographic information, data on comorbidities and COVID-19 testing results, and are encouraged to self-report a set of pre-specified symptoms on a daily basis to enable collection of longitudinal information on incident symptoms. This study was approved by the Partners Human Research Committee (Protocol 2020P000909) and King's College London ethics committee (REMAS ID 18210, LRS-19/20-18210).

Study population

Individuals were included in the study if they met the following criteria: 1) aged ≥ 18 years, 2) reported developing any symptom between March 24th and September 15th, 2020, and 3) entered a valid RT-PCR test result within the first seven days of symptom onset. App users who recorded a history of COVID-19 were excluded. Data were frozen and extracted on October 21st, 2020. UK participants served as a discovery cohort, which was randomly split into training and validation datasets of equal size. US participants served as a replication cohort to confirm the generalisability of the results. Both cohorts were stratified by age (18-54 and ≥ 55 years) to align with age strata in ongoing COVID-19 vaccine efficacy trials.

Methods

Data analyses

Symptoms recorded within three and seven days of symptom onset were included in the analyses (see **Supplementary Table 1** for complete list of symptoms and corresponding questions participants were asked). Analysis of symptoms within the first three days is key to enable testing for SARS-CoV-2 soon after symptom onset while viral load is highest. An additional buffer for inclusion of symptoms within seven days was also used, which may be important to detect development of lower respiratory tract signs indicative of pneumonia. Anosmia and ageusia were considered one symptom in the reporting app.

Participants were classified as symptom-screening positive when they recorded at least one of the symptoms in the symptom combination concerned. This was compared with self-reported RT-PCR results considered the gold standard for COVID-19 case detection. If multiple positive RT-PCR test results were recorded for an individual, only the first was included.

A COVID-19 case was defined as a newly symptomatic individual with a first ever positive RT-PCR test result. For individual symptoms or symptom combinations, three evaluation parameters were considered, taking disease status to be a positive RT-PCR test: 1) sensitivity, computed as the percentage of COVID-19 positive individuals correctly identified, 2) specificity, calculated as the percentage of individuals correctly classified as COVID-19 negative, and 3) the reciprocal of precision, that is the number of RT-PCR tests needed to identify one RT-PCR positive COVID-19 case (i.e. Tests Per Case [TPC]).

Multi-objective evolutionary optimization

As sensitivity and specificity of a given symptom combination represent conflicting objectives, a multi-objective evolutionary algorithm (MOEA) was used to generate optimal symptom combinations from the data, each characterised by a good trade-off between specificity and sensitivity. Optimisation problems with multiple objectives have a set of optimal solutions (i.e., Pareto-optimal solutions) rather than one single optimal solution. No Pareto-optimal solution is better than the other without further information on the specific objective to be addressed. For MOEA, we employed the well-known NSGAI¹⁷ developed in the python package pymoo v0.4.2.1. The optimal set of parameters were derived through experimenting with different values (see **Supplementary Table 2** for parameter information). The training and validation datasets were used to generate and evaluate the Pareto-optimal symptom combinations (referred to as data-inferred symptom combinations).

Evaluation of individual symptoms and symptom combinations

Sensitivity, specificity, and TPC were evaluated for each individual symptom and symptom combinations using the validation dataset. We considered symptom combinations derived from both clinical experience/guidance (i.e., clinically inferred symptom combinations) and generated from the data using the MOEA (i.e., data-inferred symptom combinations). All evaluations were repeated on the US-replication cohort and on the data stratified by age.

For clinically-inferred symptom combinations we evaluated: 1) respiratory symptoms (cough, dyspnoea), 2) WHO-defined pneumonia symptoms (cough, dyspnoea, fever), 3) COVID-19 specific symptoms as defined by Public Health England (PHE) (fever, cough, dyspnoea, anosmia/ageusia), and 4) extended symptoms (fever, cough, dyspnoea, anosmia/ageusia, fatigue, headache). This latter category was added post-hoc after exploration of the app data indicated high sensitivity of headache and fatigue in other contexts.¹⁸

Regarding data-inferred symptom combinations, among all the generated combinations, we evaluated the one with highest sensitivity, the one with a sensitivity of ~90%, and the one characterised by a specificity of ~50%, which is of interest from a clinical standpoint.

Results

A total of 122,305 individuals were included in the UK-discovery cohort, of which 1,202 tested COVID-19 positive. In the US-replication cohort, 3,162 individuals were included, of which 79 tested COVID-19 positive. The patient selection flow charts are displayed in **Supplementary Figure 1** and **2**. **Table 1** shows the demographic characteristics of the population.

Table 1. Demographics of study population

	UK-discovery cohort		US-replication cohort	
	C-19 RT-PCR positive	C-19 RT-PCR negative	C-19 RT-PCR positive	C-19 RT-PCR negative
Total number	1,202	121,103	79	3,083
Male (%)	25.1%	25.3%	16.0%	17.5%
Mean age, years (SD)	44.3 (12.5)	48.5 (13.0)	52.7 (13.3)	53.8 (14.7)
Mean BMI (SD)	26.9 (5.75)	27.3 (5.5)	27.6 (6.4)	27.9 (6.0)

BMI = Body mass index; C-19 = COVID-19; RT-PCR = Reverse transcription polymerase chain reaction; SD = Standard deviation

Evaluation of individual symptoms

The sensitivity, specificity, and TPC for each individual symptom reported within three and seven days of symptom onset are displayed in **Table 2**. Using the UK-discovery cohort, the individual symptoms with the highest sensitivity in both three- and seven-day analyses were headache and fatigue (67% and 65% for three-day analysis and 75% and 78% for seven-day analyses). Similar results were obtained with data from the US-replication cohort and when data were stratified by age. The sensitivity of anosmia/ageusia in the UK-discovery cohort was only 22% and 49% in the three- and seven days analyses, respectively. Anosmia/ageusia, however, had the lowest TPC (20 and 10 for three- and seven-day analyses, respectively).

Table 2. Sensitivity, specificity, and TPC for each individual symptom computed on the UK-discovery cohort

Symptom	Age group	3-day analysis						7-day analysis					
		Sensitivity (%)		Specificity (%)		TPC		Sensitivity (%)		Specificity (%)		TPC	
		UK	US	UK	US	UK	US	UK	US	UK	US	UK	US
Headache	All	66.8	70.9	52.4	49.7	76	30	75.6	81.0	48.3	45.4	70	29
	[18-54]	67.8	73.8	50.7	48.6	67	27	76.9	83.3	46.2	43.1	62	27
	[55+]	63.1	67.6	55.8	50.7	111	34	71.2	78.4	52.6	47.5	102	31
Fatigue	All	64.9	73.4	53.7	47.2	76	31	77.8	87.3	49.7	42.8	66	28
	[18-54]	64.2	71.4	53.5	49.5	66	28	76.9	92.9	49.2	44.6	58	24
	[55+]	67.5	75.7	53.9	45.1	108	34	81.2	81.1	50.7	41.0	93	34
Sore throat	All	47.3	36.7	59.1	59.1	92	47	54.8	49.4	55.8	55.9	82	38
	[18-54]	48.6	45.2	56.1	53.8	83	40	55.3	54.8	52.4	49.9	76	36
	[55+]	42.9	27.0	65.4	64.2	127	60	53.1	43.2	62.9	61.6	107	41
Persistent cough	All	35.9	55.7	86.3	76.5	41	18	43.4	65.8	84.6	73.1	37	18
	[18-54]	35.8	50.0	85.6	78.2	37	18	42.9	61.9	83.8	74.4	34	17
	[55+]	36.1	62.2	87.6	74.9	55	19	45.4	70.3	86.2	71.8	47	19
Fever	All	35.3	34.2	88.9	86.6	34	17	44.8	49.4	87.0	83.4	30	15
	[18-54]	35.8	35.7	88.4	86.5	30	15	45.0	47.6	86.3	82.6	27	15
	[55+]	33.3	32.4	89.9	86.7	48	19	44.2	51.4	88.4	84.1	41	15
Myalgia	All	32.2	43.0	86.1	82.9	46	17	43.8	59.5	84.2	79.6	37	15
	[18-54]	32.8	42.9	86.2	85.1	39	14	44.8	61.9	84.2	81.8	32	12
	[55+]	30.2	43.2	85.7	80.8	75	21	40.4	56.8	84.1	77.6	61	19
Hoarse voice	All	23.7	31.6	89.9	88.0	46	17	33.7	44.3	88.0	84.8	37	15
	[18-54]	23.1	33.3	89.9	87.6	41	15	33.4	40.5	87.8	84.4	33	16
	[55+]	25.8	29.7	90.0	88.4	62	19	34.6	48.6	88.4	85.2	52	15
Skipped meals	All	22.8	34.2	88.9	80.1	52	25	33.0	57.0	87.5	77.0	39	18
	[18-54]	22.5	38.1	89.1	82.5	45	18	32.4	54.8	87.5	79.3	35	15
	[55+]	23.8	29.7	88.6	77.8	76	34	35.4	59.5	87.5	74.8	55	20
Chest pain	All	22.5	21.5	89.1	86.3	52	27	33.7	32.9	87.4	83.0	39	22
	[18-54]	23.1	14.3	88.6	85.9	46	38	34.3	28.6	86.6	81.3	35	26
	[55+]	20.6	29.7	90.1	86.7	76	21	31.5	37.8	88.9	84.5	54	19
Anosmia/ageusia	All	21.8	13.9	96.1	95.7	20	14	48.7	46.8	95.4	94.7	10	6
	[18-54]	22.9	9.5	95.8	95.4	17	19	51.3	47.6	95.0	94.2	9	6
	[55+]	17.5	18.9	96.7	96.0	30	10	39.2	45.9	96.2	95.1	16	6
Dyspnoea	All	20.4	22.8	89.9	86.1	53	26	32.3	39.2	88.0	83.1	38	19
	[18-54]	21.3	19.0	90.0	86.3	43	28	33.3	40.5	87.9	82.5	32	17
	[55+]	17.1	27.0	89.8	85.9	95	24	28.5	37.8	88.3	83.7	64	20
Diarrhoea	All	19.1	19.0	82.5	76.8	97	51	27.1	38.0	80.3	72.9	74	30
	[18-54]	19.7	16.7	82.5	76.9	81	53	28.0	38.1	80.1	72.7	63	28
	[55+]	16.7	21.6	82.5	76.6	165	50	23.8	37.8	80.8	73.0	123	33
Abdominal pain	All	14.1	16.5	83.4	82.2	124	45	21.3	31.6	81.3	79.5	90	28
	[18-54]	13.6	19.0	83.6	84.1	110	33	21.7	31.0	81.3	81.3	76	24
	[55+]	15.9	13.5	82.9	80.4	169	66	20.0	32.4	81.2	77.9	143	32
Delirium	All	8.5	12.7	92.4	89.9	95	34	13.5	26.6	91.2	87.8	66	20
	[18-54]	8.3	14.3	92.9	90.4	79	26	13.4	21.4	91.7	87.7	55	23
	[55+]	9.1	10.8	91.4	89.4	148	45	13.8	32.4	90.4	87.8	107	18

TPC = Tests per case

These results are confirmed by **Figure 1**, which displays the frequency of the symptoms for the UK-discovery cohort for both COVID-19 positive and negative cases.

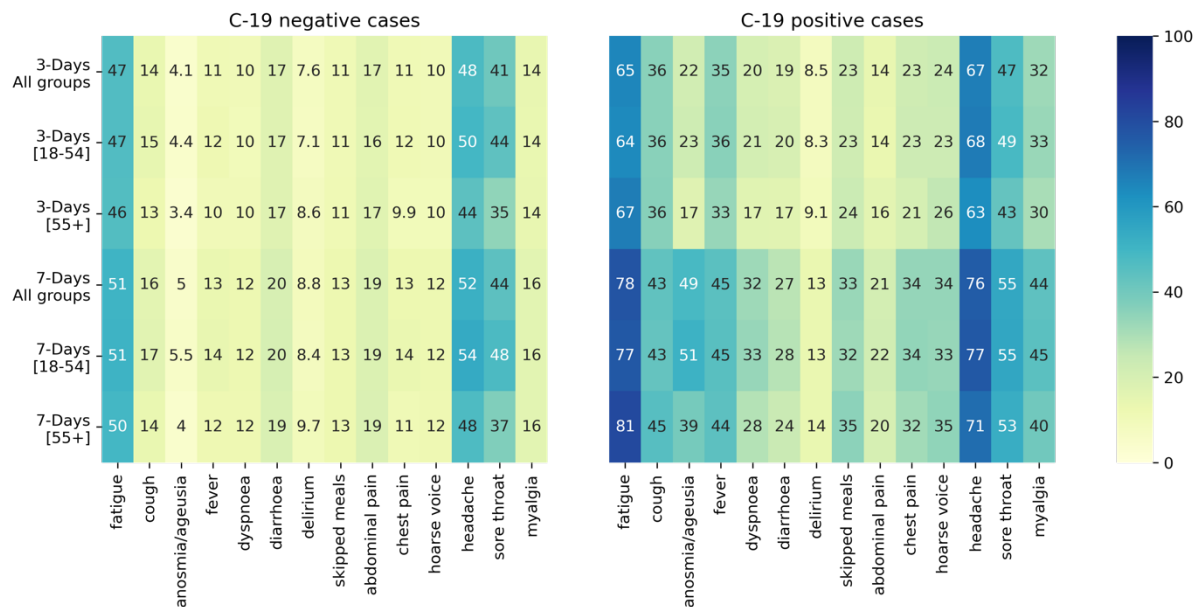


Figure 1. Symptom frequency for COVID-19 negative (left) and COVID-19 positive (right) cases

Evaluation of symptom combinations

The sensitivity, specificity, and TPC of both clinically- and data-inferred symptom combinations, computed on the UK-validation and US-replication cohorts, and reported within three and seven days of symptom onset are displayed in **Table 3**.

Cough or dyspnoea were reported by 46% of individuals positive for COVID-19 within the first three days of symptom onset. The addition of fever (i.e., WHO-defined pneumonia symptom combination) increased sensitivity to 60%, while the further addition of anosmia/ageusia (i.e., PHE COVID-19 specific symptom combination) increased sensitivity to 69%. When headache and fatigue are added, (i.e., extended symptom combination) the proportion of COVID-19 cases identified increased to 92% but the TPC doubled compared to the respiratory symptom combination (42 versus 85). Similarly, within seven days of symptom onset, COVID-19 specific and extended symptom combination were reported in 84% and 97% of RT-PCR positive cases, at the cost of 42 and 81 TPC, respectively. Similar results were obtained when data were stratified by age. The sensitivity estimates from the US-replication cohort were higher for all four combinations; extended symptom combination estimates

reached 96% and 99% for the three- and seven-day analyses, respectively. On the contrary, the specificity decreased to 21% and 18%, although TPC values were lower for the US-replication cohort.

Table 3. Sensitivity, specificity, and TPC for the clinically and data-inferred combinations of symptoms, computed on the held-out validation dataset

	Symptom	Age group	Three-day analysis						Seven-day analysis					
			Sensitivity (%)		Specificity (%)		TPC		Sensitivity (%)		Specificity (%)		TPC	
			UK	US	UK	US	UK	US	UK	US	UK	US	UK	US
Clinically inferred symptoms	Respiratory symptoms ¹	All	46.4	48.1	81.9	76.6	42	21	58.1	64.6	79.1	72.3	37	19
		[18-54]	47.1	45.2	81.6	76.8	37	20	58.5	64.3	78.5	71.6	33	18
		[55+]	44.3	51.4	82.5	76.5	60	22	56.7	64.9	80.4	73.0	51	20
	WHO defined pneumonia ²	All	59.8	74.7	71.7	59.5	51	23	71.4	84.8	68.4	54.5	46	23
		[18-54]	59.9	69.0	71.0	61.3	46	22	70.7	83.3	67.4	55.5	42	21
		[55+]	59.5	81.1	73.2	57.8	68	24	73.9	86.5	70.6	53.6	59	25
	C-19-specific symptoms ³	All	69.0	79.7	69.6	57.6	47	23	83.7	92.4	66.2	52.6	42	22
		[18-54]	69.5	73.8	68.8	59.5	42	22	84.4	92.9	65.1	53.8	37	20
		[55+]	67.2	86.5	71.4	55.7	64	24	81.3	91.9	68.7	51.4	57	25
	Extended symptoms ⁴	All	92.0	96.2	25.9	21.1	85	35	96.7	98.7	22.9	17.9	81	35
		[18-54]	92.6	95.2	25.0	22.2	76	32	96.6	100.0	21.7	18.6	72	32
		[55+]	90.1	97.3	27.9	20.1	120	38	97.0	97.3	25.6	17.3	112	39
Data-inferred subsets	Combination with highest sensitivity ⁵	All	96.3	96.2	11.9	9.8	96	40	99.2	98.7	10.4	8.2	92	39
		[18-54]	96.9	95.2	10.4	8.0	85	38	99.4	100	8.8	6.6	80	36
		[55+]	94.4	97.2	15.2	11.6	141	42	98.5	97.3	13.7	9.8	134	90
	Combination with sensitivity ~ 90% ⁶	All	92.2	96.2	22.4	15.6	89	36	94.7	96.2	37.8	29.3	68	31
		[18-54]	92.7	95.2	21.5	19.2	78	33	93.2	100	37.1	31.3	59	27
		[55+]	91.3	97.3	23.9	17.9	131	39	97.7	97.3	26.8	18.8	115	38
	Combination with specificity ~ 50% ⁷	All	76.4	84.8	40.9	40.0	72	30	87.3	91.1	49.2	38.9	59	29
		[18-54]	76.5	80.9	48.0	42.5	63	28	88.7	92.9	49.6	39.9	50	25
		[55+]	79.3	89.2	49.0	37.8	101	32	82.3	89.2	50.7	37.9	92	32

¹Cough, dyspnoea; ²Cough, dyspnoea, fever; ³Fever, cough, dyspnoea, and anosmia/ageusia; ⁴Fever, cough, dyspnoea, anosmia/ageusia, fatigue, and headache; ⁵Fatigue, anosmia/ageusia, persistent cough, diarrhoea, headache and sore throat; ⁶(3-day) Fatigue, anosmia/ageusia, persistent cough, dyspnoea, diarrhoea, headache, (7-day) fatigue, fever, anosmia/ageusia, persistent cough; ⁷ (3-day) Fatigue, fever, anosmia/ageusia, (7-day) Anosmia/ageusia, persistent cough, dyspnoea, diarrhoea, skipped meals, myalgia
TPC = Tests per case

Among data-inferred symptom combinations, the one with highest sensitivity (fatigue, anosmia/ageusia, cough, diarrhoea, headache, and sore throat) identified 96% and 99% of RT-PCR positive COVID-19 cases and required 96 and 92 TPC in the three- and seven-day analyses, respectively. The sensitivity results were similar for the US-replication cohort and by age. However, the number of tests needed for those aged ≥ 55 years increased by 30% for both the three-day and seven-day analyses.

Figure 2 displays the three data-inferred symptom combinations for both three- and seven-day analyses. Anosmia/ageusia were included in all three symptom combinations at both time points, fatigue was included in all symptom combinations for the three-day analyses, and cough

for the seven-day analyses. Headache was slightly more important when symptoms were recorded within three days of onset. Diarrhoea as an individual symptom was not predictive of a positive COVID-19 RT-PCR result but became predictive when associated with other symptoms.

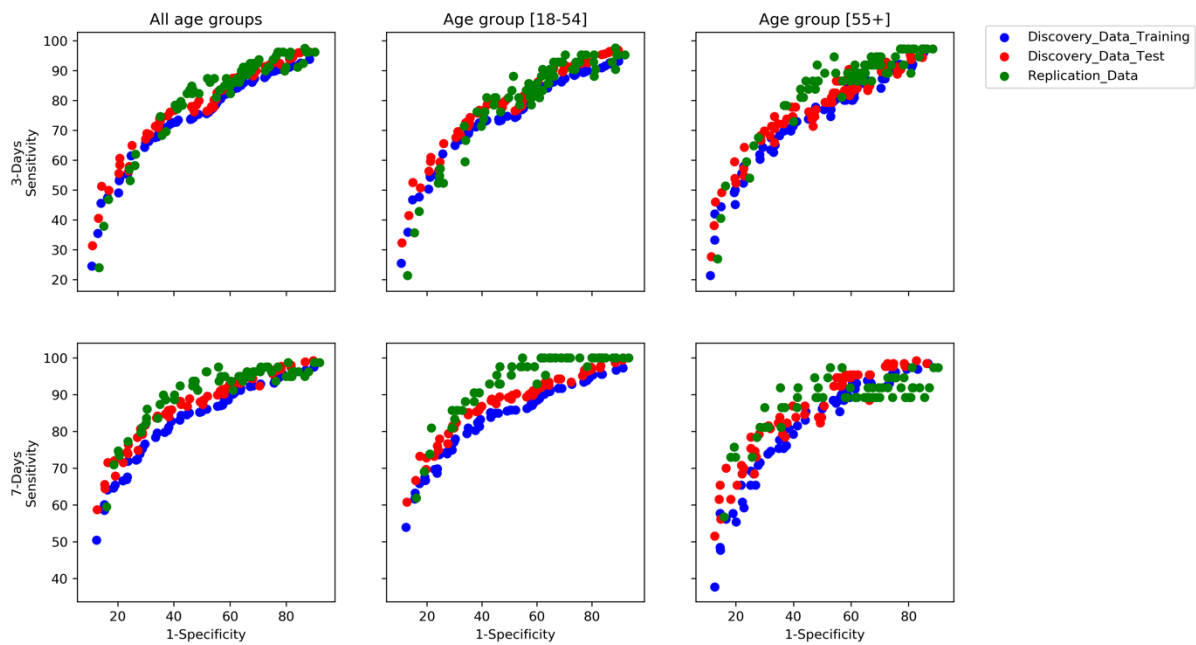
Figure 2. Combination of symptoms with highest sensitivity, sensitivity ~ 90%, and specificity ~50%

		Fatigue	Fever	Anosmia/ageusia	Cough	Dyspnoea	Diarrhoea	Delirium	Skipped meal	Abdominal pain	Chest pain	Hoarse voice	Headache	Sore throat	Myalgia
3- Days	Highest sensitivity	■		■	■		■						■	■	
	Sensitivity ~ 90%	■		■	■		■						■	■	
	Specificity ~ 50%	■	■	■											
7- Days	Highest sensitivity	■		■			■						■	■	
	Sensitivity ~ 90%	■	■	■											■
	Specificity ~ 50%			■	■	■	■		■						■

All the Pareto-optimal symptom combinations generated by the MOEA are displayed in **Figure 3**. Each point (solution) of the Pareto corresponds to a certain symptom combination with a related sensitivity, specificity, and TPC (see **Supplementary Table 4** and **5** for the complete list of solutions for three- and seven-day analyses, respectively). These generated symptom combinations achieved similar values of sensitivity and specificity for the UK-training, UK-validation, and US-replication cohorts, thus confirming the validity of this methodology. Moreover, results were also confirmed for the two age groups.

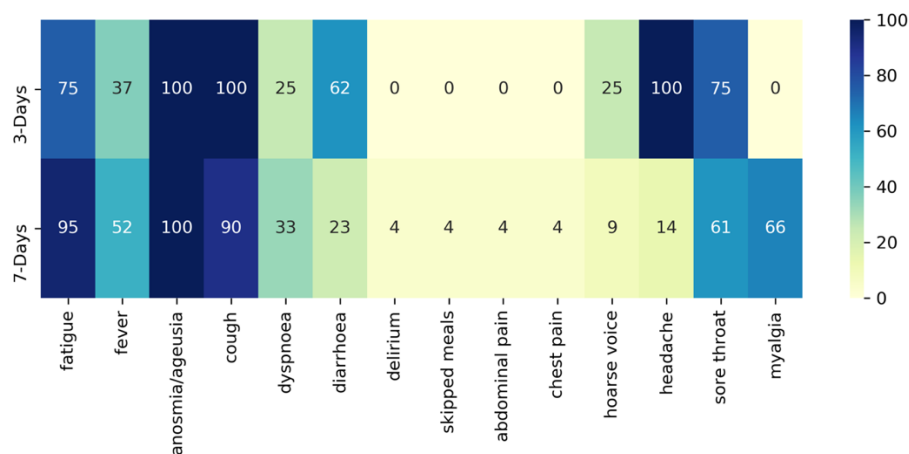
Figure 4 displays the frequency of symptoms selected in symptom combinations with a sensitivity $\geq 90\%$. Fatigue, cough, and anosmia/ageusia were present in most symptom combinations with high specificity. Diarrhoea was selected ~60% of the time for the three-day analyses.

Figure 3. Pareto of optimal subset generated by the multi-objective evolutionary algorithm for three- and seven-day analyses



Each point represents a subset of symptoms characterised by a different trade-off between sensitivity and specificity.

Figure 4. Percentage of a symptom’s appearance in symptom combinations with sensitivity ≥ 90 %



Discussion

We present data from, what is to our knowledge, the largest community-based COVID-19 symptom cohort study with the aim to quantify the contribution of various symptoms and symptom combinations associated with COVID-19 to RT-PCR positive case-finding. COVID-19 symptoms and RT-PCR test results were collected prospectively which allowed us to select

newly symptomatic individuals and simulate a clinical trial situation in which RT-PCR tests are typically conducted within three days after symptom onset. We confirm the significance of symptoms (fever, cough, anosmia/ageusia) widely considered important for triggering a RT-PCR test and extend this to include additional symptoms (fatigue, sore throat, headache, diarrhoea). The proposed approach enables the selection of symptom combinations to maximise the capture of cases without overwhelming laboratory capacity. Our findings may help to optimise the choice of triggering symptoms for diagnostic work-up in COVID-19 vaccine efficacy trials or in a wider public health setting.

In an efficacy trial, it is important to capture all COVID-19 cases with pulmonary involvement as signs/symptoms of pneumonia define moderate or severe COVID-19. Therefore, the signs/symptoms that characterise WHO-defined COVID-19 pneumonia (fever, cough, dyspnoea, tachypnoea) should trigger diagnostic work-up in a trial participant.¹⁹ Additionally, anosmia/ageusia have the highest sensitivity of all reported COVID-19 symptoms.^{9,20} Although our findings support the inclusion of these COVID-19 specific symptoms, they also show that this combination correctly identified only 69% and 83% of COVID-19 cases in the three- and seven-days analyses. This has important implications in terms of cases missed as the COVID-specific symptoms align with the current PHE definition of a possible COVID-19 case.²¹ We found that the addition of headache and fatigue (i.e., extended symptoms) increased the proportion of COVID-19 cases correctly identified to 92% but also almost doubled the TPC (from 47 to 85). Thus, an increase in sensitivity comes at a cost.

Application of MOEA identified fatigue, anosmia/ageusia, cough, diarrhoea, headache, and sore throat as the symptom combination with the highest sensitivity in three- and seven-day analyses. Diarrhoea and sore throat were identified as symptoms that may increase case finding in an efficient way, in addition to those symptoms already considered important for triggering an RT-PCR test. In situations where there is a limited testing capacity, we provide a range of optimal symptom combinations that could be used, given different target numbers of TPC identified. This finding may prove useful for COVID-19 vaccine developers or in public health settings when deciding which symptoms should trigger testing to optimise financial and logistical resource utilisation. Importantly, all the symptoms that constitute the combination with the highest sensitivity have been included as triggering symptoms in publicly available clinical trial protocols of ongoing vaccine efficacy trials.⁹⁻¹⁴

Few studies have been published that assess COVID-19 symptoms in community-based cohorts. Menni et al. presented results using data generated from this COVID-19 Symptom Study app; however, the aim was different and only data from March-April 2020 were included.²² We extend these data to September 2020 and, importantly, consider the results from the perspective of a potential COVID-19 vaccine developer. Menni et al. suggest anosmia/ageusia, fatigue, persistent cough, and loss of appetite might together identify individuals with COVID-19.²² A separate COVID-19 symptom app from Germany suggests nausea and vomiting have a stronger predictive value for COVID-19 infection than symptoms such as sore throat or persistent cough.²³ Thus, both studies identify gastrointestinal symptoms as important in identifying cases of COVID-19. Our study reports similar findings with diarrhoea found to be important to case finding. More recently, in another community-based observational study, sensitivity, specificity, and positive and negative predictive values were reported for retrospectively collected symptoms and symptom combinations that occurred during the 14-day period prior to screening for SARS-CoV-2 infection in a US seroprevalence study.²⁴ The two symptom clusters most associated with SARS-CoV-2 infection were: 1) ageusia, anosmia, and fever, and 2) shortness of breath, cough, and chest pain. In our study, dyspnoea was rarely and chest pain never selected as part of an efficient symptom combination likely due to dyspnoea often occurring later in the disease course.²⁵ The sensitivity of dyspnoea increased in the seven-day compared to three-day analyses. However, the importance of dyspnoea as a symptom of pulmonary involvement makes it a critical triggering symptom in vaccine efficacy trials. Tachypnoea, which is included in the WHO-defined definition for pneumonia, was not captured as a symptom in the app per se; however, it likely co-occurs with dyspnoea. Headache and diarrhoea were more likely to be selected in the three-day scenario and fever during the seven-day scenario again, reflecting different timings of symptoms in the disease course.

The sensitivity of symptoms and various clinically inferred symptom combinations were similar for the age groups (18-54 and ≥ 55 years); however, the TPC was higher in the ≥ 55 years age group. This suggests self-reporting may work better for younger than older individuals. The sensitivity, specificity, and TPC computed on the US-replication cohort were higher than for the UK-discovery cohort possibly due to different testing practices and public health measures adopted in each country. It will be important for these findings to be validated in low- and middle-income country (LMIC) settings as COVID-19 vaccine efficacy trials are likely to be conducted in high income countries as well as LMICs. Vaccine developers should take into

account regional considerations such as background incidence of co-infection and other trial-related aspects when interpreting these results.

This study has many strengths, including the large sample size and cost-effectiveness of the data source. Also, our study is community-based and adds important data as most studies that have assessed symptoms in COVID-19 have involved hospital-based populations. Some limitations, however, also need consideration. First, the results are based on data self-reported through a mobile app and therefore biased towards people with smartphone access. However, the app included a feature to enable reporting on behalf of someone else given their consent. Second, reported test results were not externally verified, however, antigen tests were not available during the study period, thus minimising risk of participant confusion regarding precise swab tests. As the precise RT-PCR used was not recorded and likely varied between participants, false positive rates were not known and results taken at face value. A further limitation is that app users may not be representative of the wider population. Finally, these data were generated in the spring and summer months when the incidence of concurrent respiratory infections (e.g., influenza) is low. The latter may have implications for trials conducted in winter.

In summary, we confirm the significance of symptoms widely recommended for triggering RT-PCR and identified additional symptom combinations to enable efficient trade-off between the number of positive cases detected and tests needed. Our findings may help optimise the choice of triggering symptoms for diagnostic work-up in COVID-19 vaccine efficacy trials and also have wider public health implications.

Conflicts of interests

Potential conflicts of interest. JW, RD, JCP, and AM are employees of Zoe Global Ltd. ATC reports grants from Massachusetts Consortium on Pathogen Readiness during the conduct of the study, personal fees from Pfizer Inc., and grants and personal fees from Bayer Pharma; CEPI (authors AC, JG, JPC, AEL) funds clinical trials of COVID-19 vaccines. All other authors declare no competing interests.

Funding

This work was supported by Zoe Global Limited; Department of Health; Wellcome Trust; Engineering and Physical Sciences Research Council (EPSRC); National Institute for Health Research (NIHR); Medical Research Council (MRC); Alzheimer's Society; Massachusetts Consortium for Pathogen Readiness (MassCPR); and Coalition for Epidemic Preparedness Innovations (CEPI).

Acknowledgements

Zoe provided in kind support for all aspects of building, running and supporting the app and service to all users worldwide. CEPI provided funding for the analysis of the data. Support for this study was provided by the NIHR-funded Biomedical Research Centre based at GSTT NHS Foundation Trust. Investigators also received support from the Wellcome Trust, the MRC/BHF, Alzheimer's Society, EU, NIHR, CDRF, and the NIHR-funded BioResource, Clinical Research Facility and BRC based at GSTT NHS Foundation Trust in partnership with KCL, the UK Research and Innovation London Medical Imaging & Artificial Intelligence Centre for Value Based Healthcare, the Wellcome Flagship Programme (WT213038/Z/18/Z), the Chronic Disease Research Foundation, and DHSC. DAD is supported by the National Institute of Diabetes and Digestive and Kidney Diseases K01DK120742 and by the American Gastroenterological Association AGA-Takeda COVID-19 Rapid Response Research Award (AGA2021-5102). ATC was supported in this work through a Stuart and Suzanne Steele MGH Research Scholar Award. The Massachusetts Consortium on Pathogen Readiness (MassCPR) and Mark and Lisa Schwartz supported MGH investigators (LHN, DAD, ADJ, ATC).

References

1. Hodgson SH, Mansatta K, Mallett G, Harris V, Emary KRW, Pollard AJ. What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. *Lancet Infect Dis* 2020; S1473-3099(20):30773–8.
2. Corey L, Mascola JR, Fauci AS, Collins FS. A strategic approach to COVID-19 vaccine R&D. *Science* 2020; 368(6494):948–950.
3. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *New England Journal of Medicine*, December 2020, doi = {10.1056/NEJMoa2034577}.

4. Moderna Announces Primary Efficacy Analysis in Phase 3 COVE Study for Its COVID-19 Vaccine: <https://investors.modernatx.com/node/10421/pdf> [Accessed 9th December 2020].
5. AZD1222 vaccine met primary efficacy endpoint in preventing COVID-19: <https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222h1r.html> [Accessed 9th December 2020].
6. Petersen I, Phillips A. Three Quarters of People with SARS-CoV-2 Infection are Asymptomatic: Analysis of English Household Survey Data. *Clin Epidemiol.* 2020;12:1039–1043.
7. Pormohammad A, Ghorbani S, Khatami A, et al. Comparison of influenza type A and B with COVID-19: A global systematic review and meta-analysis on clinical, laboratory and radiographic findings. *Rev Med Virol.* 2020:e2179.
8. Wiersinga JW, Rhodes A, Cheng AC, et al. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA.* 2020;324(8):782–793.
9. Haehner A, Drafi J, Drager S, de With K, Hummel T. Predictive value of sudden olfactory loss in the diagnosis of COVID-19. *ORL J Otor. Relat Spec* 2020;82(4):175–180.
10. A Phase 3, Randomised, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older. <https://www.modernatx.com/sites/default/files/mRNA-1273-P301-Protocol.pdf>
11. A phase 1/2/3, placebo-controlled, randomised, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals https://pfe-pfizer.com-d8-prod.s3.amazonaws.com/2020-09/C4591001_Clinical_Protocol_0.pdf
12. A Randomised, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older. <https://www.jnj.com/coronavirus/covid-19-phase-3-study-clinical-protocol>
13. A Phase III Randomized, Double-blind, Placebo-controlled Multicenter Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19. https://s3.amazonaws.com/ctr-med-7111/D8110C00001/52bec400-80f6-4c1b-8791-0483923d0867/c8070a4e-6a9d-46f9-8c32-cece903592b9/D8110C00001_CSP-v2.pdf

14. A Phase 3, Randomised, Observer-blinded, Placebo-Controlled Trial to evaluate the Efficacy and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-RS) with Matrix-M1 Adjuvant in Adult participants 18-84 years of Age in the United Kingdom.
<https://www.novavax.com/download/files/protocols/2019nCoV302Phase3UKVersion2FinalCleanRedacted.pdf>
15. Voysey M, Costa SU, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2020; DOI:[https://doi.org/10.1016/S0140-6736\(20\)32661-1](https://doi.org/10.1016/S0140-6736(20)32661-1)
16. Drew DA, Nguyen LH, Steves CJ, et al. Rapid implementation of mobile technology for real-time epidemiology of COVID-19. *Science* 2020;368(6497):1362–1367.
17. Deb K, Pratap A, Agarwal S, Meyarivan T. A fast and elitist multi-objective genetic algorithm: NSGA-II *IEEE. Transactions on Evolutionary Computation* 2002;6:182–97.
18. Sudre CH, Lee K, Lochlainn MN. Symptom clusters in Covid19: A potential clinical prediction tool from the COVID Symptom study App. *medRxiv* Jun 16; 2020.06.12.20129056. doi: 10.1101/2020.06.12.20129056. Preprint
19. Clinical Management of COVID-19 (WHO interim guidance): <https://www.who.int/publications/i/item/clinical-management-of-covid-19> (Accessed November 22, 2020).
20. Agyeman AA, Chin KL, Landersdorfer CB. Smell and Taste Dysfunction in Patients With COVID-19: A systematic review and meta-analysis. *Mayo Clin Proc.* 2020;95(8):1621–1631.
21. Public Health England. <https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases/investigation-and-initial-clinical-management-of-possible-cases-of-wuhan-novel-coronavirus-wn-cov-infection#criteria> (Accessed December 11th 2020).
22. Menni C, Valdes AM, Freidin MB, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. *Nat Med.* 2020;26(7):1037–1040.
23. Zens M, Brammertz A, Herpich J, et al. App-based tracking of self-reported COVID-19 symptoms: analysis of questionnaire data. *J Med Internet Res.* 2020;22(9):e21956.
24. Dixon BE, Wools-Kaloustian K, Fadel WF, et al. Symptoms and symptom clusters associated with SARS-CoV-2 infection in community-based populations: Results from a

statewide epidemiological study. medRxiv Oct 22;2020.10.11.20210922. doi: 10.1101/2020.10.11.20210922. Preprint

25. Tang D, Comish P, Kang R. The hallmarks of COVID-19 disease. PLoS Pathog 2020;16(5): e10085

Supplementary tables

Supplementary Table 1. List of self-reported symptoms and corresponding question used in the reporting app

Symptoms	Question
Fatigue	Are you experiencing unusual fatigue?
Anosmia/ageusia	Do you have a loss of smell/taste?
Cough	Do you have a persistent cough
Dyspnoea	Are you experiencing unusual shortness of breath?
Diarrhoea	Are you experiencing diarrhoea?
Delirium	Do you have any of the following symptoms: confusion, disorientation, or drowsiness?
Skipped meals	Have you been skipping meals?
Abdominal pain	Do you have an unusual abdominal pain?
Chest pain	Are you feeling an unusual chest pain or tightness in your chest?
Hoarse voice	Do you have an unusually hoarse voice?
Headache	Do you have a headache?
Sore throat	Do you have a sore throat?
Myalgia	Do you have unusual strong muscle pains?

Supplementary Table 2. NSGAI parameters

Parameter	Value
Population size	80
Number of offspring	40
Total number of generations	500
Parent selection	Tournament Selection
Crossover	Two-point crossover
Crossover probability	0.9
Mutation	Random flip
Mutation probability	0.1

Supplementary Table 3. Sensitivity, specificity, and TPC for the four clinically inferred symptom combinations computed on the UK-discovery cohort

Symptom	Age group	3-day analysis						7-day analysis					
		Sensitivity (%)		Specificity (%)		TPC		Sensitivity (%)		Specificity (%)		TPC	
		UK	US	UK	US	UK	US	UK	US	UK	US	UK	US
Respiratory symptoms ¹	All	44.7	48.1	81.9	76.6	43	21	57.7	64.6	79.1	72.3	38	19
	[18-54]	45.2	45.2	81.6	76.8	38	20	58.2	64.3	78.4	71.6	33	18
	[55+]	42.9	51.4	82.7	76.5	64	22	55.8	64.9	80.5	73.0	54	20
WHO-defined pneumonia ²	All	58.8	74.7	71.9	59.5	51	23	70.3	84.8	68.5	54.5	46	23
	[18-54]	59.2	69.0	71.1	61.3	45	22	70.5	83.3	67.5	55.5	41	21
	[55+]	57.5	81.1	73.3	57.8	73	24	69.6	86.5	70.7	53.6	65	25
COVID-19-specific symptoms ³	All	67.4	79.7	69.8	57.6	48	23	81.0	92.4	66.4	52.6	43	22
	[18-54]	68.1	73.8	69.0	59.5	42	22	82.0	92.9	65.3	53.8	38	20
	[55+]	65.1	86.5	71.5	55.7	69	24	77.7	91.9	68.8	51.4	62	25
Extended Symptoms ⁴	All	90.7	96.2	26.0	21.1	86	35	95.5	98.7	23.0	17.9	82	35
	[18-54]	91.2	95.2	25.0	22.2	75	32	95.5	100.0	21.7	18.6	72	32
	[55+]	88.9	97.3	28.1	20.1	128	38	95.4	97.3	25.7	17.3	119	39

¹Cough, dyspnoea; ²Cough, dyspnoea, fever; ³Fever, cough, dyspnoea, and anosmia/ageusia; ⁴Fever, cough, dyspnoea, anosmia/ageusia, fatigue, and headache
TPC = Tests per case

Supplementary Table 4. Pareto of optimal combination of symptoms for three-day analysis computed on the UK-discovery training data, ordered by decreasing sensitivity

Symptom combinations	Sensitivity	Specificity	TPC
fatigue, anosmia/ageusia, cough, diarrhoea, headache, sore throat	93.8	11.8	88
fatigue, fever, anosmia/ageusia, cough, headache, sore throat	92.5	14.9	85
fatigue, anosmia/ageusia, cough, dyspnoea, headache, sore throat	92.2	15.3	85
fatigue, anosmia/ageusia, cough, hoarse voice, headache, sore throat	92.0	15.5	85
fever, anosmia/ageusia, cough, diarrhoea, headache, sore throat	91.7	17.8	82
anosmia/ageusia, cough, diarrhoea, hoarse voice, headache, sore throat	91.2	18.9	81
fatigue, fever, anosmia/ageusia, cough, diarrhoea, headache	90.6	22.4	78
fatigue, anosmia/ageusia, cough, dyspnoea, diarrhoea, headache	90.5	22.7	77
fatigue, anosmia/ageusia, cough, chest pain, sore throat, unusual muscle pains	89.9	24.0	76
fatigue, anosmia/ageusia, cough, dyspnoea, sore throat, unusual muscle pains	89.8	24.7	75
fatigue, fever, anosmia/ageusia, cough, dyspnoea, headache	89.4	26.1	74
fatigue, fever, anosmia/ageusia, cough, delirium, headache	88.6	26.9	73
fatigue, fever, anosmia/ageusia, cough, headache	88.4	27.3	73
fatigue, anosmia/ageusia, cough, dyspnoea, headache	87.7	27.7	72
fever, anosmia/ageusia, cough, dyspnoea, diarrhoea, headache	87.3	31.3	69

anosmia/ageusia, cough, dyspnoea, diarrhoea, hoarse voice, headache	87.0	31.7	68
fever, anosmia/ageusia, cough, diarrhoea, delirium, headache	86.7	31.9	68
anosmia/ageusia, cough, diarrhoea, delirium, hoarse voice, headache	86.1	32.2	68
anosmia/ageusia, cough, dyspnoea, hoarse voice, headache, unusual muscle pains	86.0	35.2	65
fever, anosmia/ageusia, cough, dyspnoea, hoarse voice, headache	85.8	35.8	64
fever, anosmia/ageusia, cough, delirium, hoarse voice, headache	85.1	36.1	64
fever, anosmia/ageusia, cough, dyspnoea, delirium, headache	84.9	36.4	64
anosmia/ageusia, cough, dyspnoea, delirium, hoarse voice, headache	84.6	37.2	63
anosmia/ageusia, cough, hoarse voice, headache, unusual muscle pains	84.2	37.4	63
fever, anosmia/ageusia, cough, dyspnoea, headache	84.1	38.3	62
anosmia/ageusia, cough, dyspnoea, hoarse voice, headache	83.7	39.2	61
fatigue, fever, anosmia/ageusia, cough, dyspnoea, unusual muscle pains	83.5	40.0	60
fatigue, anosmia/ageusia, cough, dyspnoea, hoarse voice, unusual muscle pains	83.2	40.3	60
fatigue, anosmia/ageusia, cough, dyspnoea, chest pain, unusual muscle pains	82.5	40.7	59
fatigue, fever, anosmia/ageusia, cough, dyspnoea, delirium	82.1	41.6	58
fatigue, fever, anosmia/ageusia, cough, dyspnoea	82.0	42.3	58
fatigue, anosmia/ageusia, cough, dyspnoea, unusual muscle pains	81.5	42.8	57
fatigue, fever, anosmia/ageusia, cough, delirium	80.6	43.4	57
fatigue, fever, anosmia/ageusia, cough	80.2	44.1	56
fatigue, anosmia/ageusia, cough, unusual muscle pains	79.4	44.7	55
fatigue, fever, anosmia/ageusia, delirium, unusual muscle pains	78.5	45.2	55
fatigue, fever, anosmia/ageusia, unusual muscle pains	78.2	45.9	54
fatigue, fever, anosmia/ageusia, dyspnoea	77.6	46.0	54
fatigue, anosmia/ageusia, dyspnoea, unusual muscle pains	76.9	46.7	53
fatigue, fever, anosmia/ageusia, delirium	76.1	47.7	52
fatigue, fever, anosmia/ageusia	75.6	48.5	52
fever, anosmia/ageusia, cough, diarrhoea, chest pain, unusual muscle pains	75.4	51.4	49
fever, anosmia/ageusia, cough, dyspnoea, diarrhoea, unusual muscle pains	75.0	52.4	48
fever, anosmia/ageusia, cough, diarrhoea, delirium, unusual muscle pains	74.2	53.1	47
anosmia/ageusia, cough, dyspnoea, diarrhoea, hoarse voice, unusual muscle pains	74.0	53.7	46
fever, anosmia/ageusia, cough, dyspnoea, abdominal pain, unusual muscle pains	73.8	53.8	46
fever, anosmia/ageusia, cough, dyspnoea, diarrhoea, hoarse voice	73.7	54.2	46
fever, anosmia/ageusia, cough, dyspnoea, hoarse voice, unusual muscle pains	73.5	58.5	42
fever, anosmia/ageusia, cough, dyspnoea, chest pain, unusual muscle pains	72.8	59.1	41
fever, anosmia/ageusia, cough, dyspnoea, skipped meals, hoarse voice	72.6	60.1	40
anosmia/ageusia, cough, dyspnoea, chest pain, hoarse voice, unusual muscle pains	72.1	61.3	39
fever, anosmia/ageusia, cough, dyspnoea, unusual muscle pains	71.1	62.6	37
anosmia/ageusia, cough, dyspnoea, hoarse voice, unusual muscle pains	70.2	64.8	35
fever, anosmia/ageusia, cough, dyspnoea, hoarse voice	69.2	65.4	35
anosmia/ageusia, cough, dyspnoea, chest pain, unusual muscle pains	68.1	65.6	34
fever, anosmia/ageusia, cough, dyspnoea, chest pain	67.9	65.9	34
fever, anosmia/ageusia, cough, dyspnoea, delirium	67.8	65.9	34
fever, anosmia/ageusia, cough, unusual muscle pains	67.6	66.9	33

fever, anosmia/ageusia, cough, skipped meals	66.4	69.0	31
fever, anosmia/ageusia, cough, dyspnoea	65.9	70.1	30
fever, anosmia/ageusia, cough, delirium	64.3	70.5	30
fever, anosmia/ageusia, cough	61.5	75.3	25
fever, anosmia/ageusia, dyspnoea	55.8	76.4	24
fever, anosmia/ageusia, skipped meals	55.3	76.6	23
anosmia/ageusia, cough, hoarse voice	53.9	79.3	21
anosmia/ageusia, cough, dyspnoea	53.2	79.5	21
anosmia/ageusia, cough, delirium	49.0	79.7	20
fever, anosmia/ageusia	47.5	83.7	16
anosmia/ageusia, cough	45.6	85.9	14
anosmia/ageusia, hoarse voice	35.5	87.1	13
anosmia/ageusia, delirium	24.6	89.2	11

TPC = Tests per case

Supplementary Table 5. Pareto of optimal combination of symptoms for seven-day analysis computed on the UK-discovery training data, ordered by decreasing sensitivity

Symptom combinations	Sensitivity	Specificity	TPC
fatigue, anosmia/ageusia, cough, diarrhoea, headache, sore throat	97.5	93.8	90
fatigue, fever, anosmia/ageusia, cough, headache, sore throat,	96.7	91.6	87
fatigue, fever, anosmia/ageusia, cough, diarrhoea, sore throat,	96.0	87.3	82
fatigue, fever, anosmia/ageusia, cough, sore throat, unusual muscle pains	95.5	84.0	79
fatigue, anosmia/ageusia, cough, dyspnoea, sore throat, unusual muscle pains	95.0	83.7	78
fatigue, anosmia/ageusia, cough, hoarse voice, sore throat, unusual muscle pains	94.8	83.5	78
fatigue, anosmia/ageusia, cough, delirium, sore throat, unusual muscle pains	94.7	83.4	77
fatigue, anosmia/ageusia, cough, sore throat, unusual muscle pains	94.5	83.0	77
fatigue, fever, anosmia/ageusia, cough, headache	93.8	82.5	76
anosmia/ageusia, cough, dyspnoea, diarrhoea, sore throat, unusual muscle pains	92.8	77.8	71
fatigue, fever, anosmia/ageusia, cough, dyspnoea, diarrhoea	92.3	75.3	68
fatigue, fever, anosmia/ageusia, cough, abdominal pain, unusual muscle pains	92.2	74.3	67
fatigue, fever, anosmia/ageusia, cough, dyspnoea, unusual muscle pains	91.7	71.1	64
fatigue, fever, anosmia/ageusia, cough, unusual muscle pains	91.0	69.8	62
fatigue, fever, anosmia/ageusia, cough, dyspnoea	90.5	69.5	62
fatigue, anosmia/ageusia, cough, dyspnoea, unusual muscle pains	90.2	69.3	61
fatigue, fever, anosmia/ageusia, persistent cough	89.7	68.2	60
fatigue, anosmia/ageusia, cough, unusual muscle pains	89.2	68.1	59
fatigue, fever, anosmia/ageusia, unusual muscle pains	88.4	67.2	58
fatigue, fever, anosmia/ageusia, skipped meals	88.2	67.1	58
fatigue, anosmia/ageusia, persistent cough	87.0	66.5	57
fatigue, fever, anosmia/ageusia	86.9	65.4	55
fever, anosmia/ageusia, cough, dyspnoea, diarrhoea, unusual muscle pains	86.0	61.5	52
anosmia/ageusia, cough, dyspnoea, diarrhoea, hoarse voice, unusual muscle pains	85.9	60.1	50
anosmia/ageusia, cough, dyspnoea, diarrhoea, skipped meals, unusual muscle pains	85.4	59.8	50
anosmia/ageusia, cough, dyspnoea, abdominal pain, hoarse voice, unusual muscle pains	85.2	59.0	49
fever, anosmia/ageusia, cough, dyspnoea, hoarse voice, unusual muscle pains	85.0	54.8	45
anosmia/ageusia, cough, dyspnoea, skipped meals, hoarse voice, unusual muscle pains	84.5	54.1	45
anosmia/ageusia, cough, dyspnoea, chest pain, hoarse voice, unusual muscle pains	84.4	51.8	43
anosmia/ageusia, cough, dyspnoea, hoarse voice, unusual muscle pains	82.7	48.6	39
anosmia/ageusia, cough, dyspnoea, chest pain, unusual muscle pains	81.2	48.3	38
fever, anosmia/ageusia, cough, unusual muscle pains	79.7	47.5	37
anosmia/ageusia, cough, dyspnoea, chest pain, hoarse voice	79.5	44.1	34
fever, anosmia/ageusia, cough, dyspnoea	78.4	44.0	33
anosmia/ageusia, cough, dyspnoea, hoarse voice	76.5	40.0	30
anosmia/ageusia, cough, unusual muscle pains	75.4	39.4	29
anosmia/ageusia, cough, dyspnoea, chest pain	75.2	39.4	29
fever, anosmia/ageusia, persistent cough	73.9	39.0	28
anosmia/ageusia, dyspnoea, unusual muscle pains	72.4	38.6	27

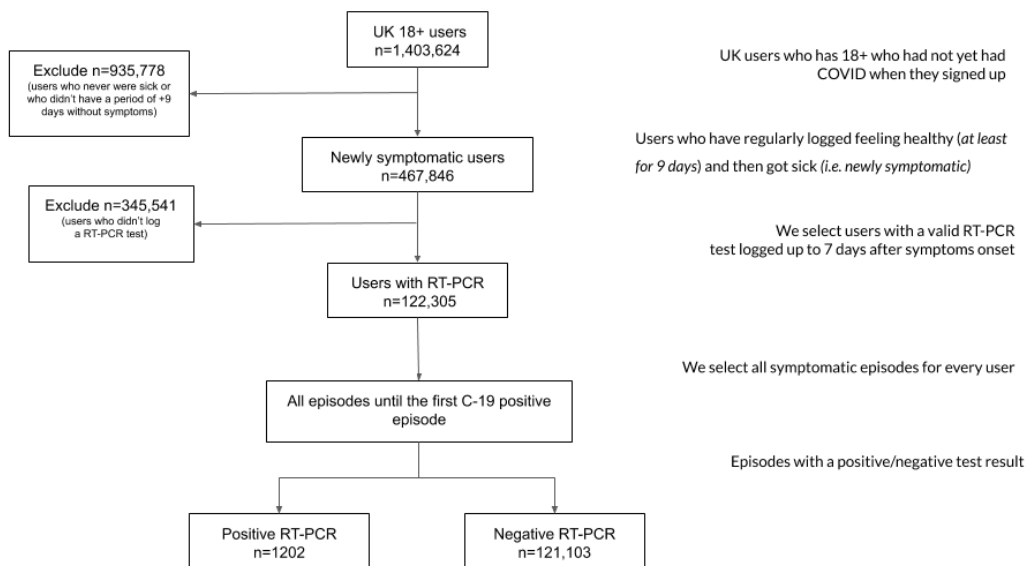
fever, anosmia/ageusia, dyspnoea	72.2	38.1	27
anosmia/ageusia, cough, dyspnoea	71.9	34.1	24
anosmia/ageusia, dyspnoea, chest pain	66.6	34.0	22
anosmia/ageusia, unusual muscle pains	65.4	30.4	19
fever, anosmia/ageusia	64.6	29.9	18
anosmia/ageusia, persistent cough	64.1	26.8	16
anosmia/ageusia, dyspnoea	60.1	26.6	15
anosmia/ageusia, delirium	50.4	25.8	12

TPC = Tests per case

Supplementary Figures

Supplementary Figure 1. Flow diagram of user selection for the UK-discovery cohort

CSS App users active from 24th of March to 15th of September 2020



Supplementary Figure 2. Flow diagram of user selection for the US-replication cohort

CSS App users active from 24th of March to 15th of September 2020

