Scientific Advisory Group

COVID-19 Scientific Advisory Group Rapid Evidence Report

COVID-19 Symptoms: Symptoms Predictive of a Positive COVID-19 Test, Duration of Symptoms, and Duration of RT-PCR and Viral Culture Positivity

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Alberta Health Services

Physical distancing works

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Lay Summary

This review determined that new partial or complete loss of taste or smell are symptoms that are quite reliably predictive of a positive COVID-19 test although the definition and assessment of symptoms varied between studies, and not all COVID-19 patients experience this. Children in particular who have a combination of

1) loss of taste/smell, 2) nausea or vomiting and 3) headache

are highly likely to test positive for COVID-19. Many other symptoms such as cough, fever, and fatigue are common in COVID-19 but are not specific to SARS-CoV-2 infection versus other causes. Children or adults presenting with one or both of a sore throat, and runny nose, without the presence of other symptoms or a known risk exposure (close contact with a person with COVID-19) are at lower risk for COVID-19. However, people with these isolated symptoms could still develop additional symptoms over time (which would mean they are more likely to test positive) and so should still isolate until symptoms resolve and get testing

Patients with COVID-19 should isolate to reduce transmission to others. Research describing how long COVID-19 symptoms last, and the results of COVID-19 testing over time results in the following suggestions for duration of isolation:

Patients who have mild or moderate symptoms should remain in isolation for 10 days from the start of symptoms to avoid transmission to others.

1) People with more severe illness (requiring hospitalization) should remain in isolation for 14 days from symptom onset, and for up to 21 days in critical illness.
2) Isolation periods may be longer for those patients who have a pre-existing conditions which cause them to be severely immunocompromised (such as a bone marrow transplant or active chemotherapy), as they may carry infectious virus for longer, and their isolation duration should be determined by a healthcare professional.

Authorship and Committee Members

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Topic: COVID-19 Symptoms: Predictors for a Positive COVID-19 Test, Clinical Resolution Duration and Duration of Detectable Virus

1. **What symptoms are predictive of a positive COVID-19 test in children and adults?**
2. **What is the typical time course of COVID-19 symptoms?**
3. **How are symptoms related to detectable virus by RT-PCR and viral culture over time? Are there symptoms which do not require ongoing quarantine?**

Context

- This review summarizes the available evidence regarding symptoms typically associated with a positive COVID-19 test, the reported duration of various COVID-19 symptoms, and the temporal relationship between onset of symptoms and virus detectability through laboratory testing procedures.
- The purpose of this review is to help inform practical decisions regarding public health measures related to symptom presentation, symptom resolution, and duration of presumed infectivity or transmissible SARS-CoV-2 infection.
- Questions have also arisen about the duration of quarantine required in individuals with different types of symptoms and negative COVID-19 reverse transcriptase polymerase chain reaction (RT-PCR) tests.

Key Messages from the Evidence Summary

Symptom data: Questions 1 and 2

- A lack of standardization of methods to assess and record symptoms and their duration introduces variability and uncertainty into studies in this area.
- Among patients in a community setting, including health care workers, the symptoms of dysosmia/anosmia and dysgeusia/ageusia (partial or complete loss of the sense of smell and taste) appear as strong, independent predictors of a positive RT-PCR COVID-19 test result in several multivariable models. While cough, fatigue, fever, headache remain common symptoms of COVID-19 these symptoms are less specific for COVID-19 than dys/anosmia and dys/ageusia.
- Multiple adjusted analyses in children and adults including health care workers also suggest that the presence of a sore throat and/or rhinorrhea decreases the odds of COVID-19 versus other causes of similar symptoms but with wide confidence intervals. In adult patients with sore throat, the absence of other symptoms reduces the probability of COVID-19 with a likelihood ratio (PLR) of 0.59 (a LR of <1 indicates a decreased probability of COVID-19 versus other causes). In a study of 592 community Health Care Workers presenting with symptoms and or exposure to COVID-19, 6.7% had isolated sore throat or nasal symptoms, with none of these having a positive RT-PCR test.
- An analysis of Alberta Public Health online symptom screening data in over 52,641 people noted a lower OR of 0.36 for a positive COVID-19 test but also noted that 4.2% of those with isolated sore throat, isolated runny nose, or both runny nose and sore throat without other symptoms had a positive COVID-19 RT-PCR. This data is

helpful but is limited by its cross-sectional nature, and the validity of the data has not been confirmed.

- In children (<18 years) the symptom combination of anosmia/ageusia, nausea/vomiting and headache increased the likelihood of COVID-19 infection, with a high PLR at 65.2. Cough and runny nose (rhinorrhea) are frequently present but are less specific for COVID-19 with PLRs of 0.96 and 0.87 respectively. In an Albertan study, over one third of children found to have a positive RT-PCR for COVID-19 were documented as asymptomatic using current assessments and definitions.
- In hospitalized patients, analyses using machine learning identified fever, cough and lung infection as the most predictive clinical presentation/symptoms of a positive RT-PCR test for COVID-19, followed by a weak relationship of runny nose and muscle soreness with COVID-19.
- Substantial variation in the duration of symptoms is reported in patients with COVID-19 related to community vs hospital settings, pediatric vs adult patient populations and inclusion of patients with different severity of illness. Few studies reported time to clinical resolution for individual symptoms. Among those that did, fever appears to resolve early, while a diminished sense of taste or smell have a longer duration
- Children generally appear to have symptom resolution within one week with a mean fever duration of 3 days and 90% having cleared all symptoms by 14 days.

Virologic data: Question 3

- Reporting of RT-PCR virus detectability duration relative to onset of symptoms varied substantially across studies. In those studies which reported both duration of symptoms and duration of RT-PCR positivity, the majority reported that symptom and clinical resolution occurred before negative RT-PCR test results. In these studies, the cycle threshold (Ct) values are lowest, representing the highest viral load and/or viral genetic material present, in the first 5-7 days after symptom onset, and cultivatable virus was not found after day 10 of symptoms in immunocompetent individuals without severe infection.
- A systematic review and meta-analysis by Cevik et al. showed an overall mean duration of RT-PCR positivity (above Ct cutoff) to be 17 days. This was found to be much shorter with a mean of 6 days for asymptomatic patients vs 12 days for symptomatic patients. The pooled mean duration of RT-PCR positivity appears to increase with severity of illness (10 days (IQR 6-15) with mild, 12 days (IQR 8-16) with moderate illness, 14 days (IQR 12-23.4) with serious illness and 32 days (IQR 16-39) with critical illness where serious illness was defined by respiratory compromise/hypoxia.
- Viral culture attempts were reported in 11 studies and in most no virus could be cultured from respiratory samples, from immunocompetent hosts, after day 8-10 of symptoms, including some samples with high viral loads (low Ct values) and some in the context of severe infection. However one study including critically ill and immunocompromised patients documented viral cultures positive between day 15-20 of symptoms. Multiple studies have shown that no cultivatable virus could be found in samples with Ct values greater than 30-40, noting however that lab thresholds for the Ct cut off vary (including across the different laboratory platforms used within Alberta) and cannot be compared quantitatively.

- In individuals with critical illness and immunocompromise, virus could very rarely be cultured up to 21 days post symptom onset. However, case reports suggest that severely immunocompromised (example, stem cell transplant, active chemotherapy, use of B cell depletion) patients can exhibit persistent culture positive infection for > 21 days.
- Studies of COVID-19 serology have demonstrated that seroconversion occurs in up to 80% of patients within 20 days of initial RT-PCR positivity regardless of the presence of residual symptoms. Seroconversion with neutralizing antibody is more likely to occur sooner in patients with more severe disease and appears to be maintained for at least four months. Asymptomatic patients appear to have a lower, later and less durable rate of seroconversion. Seroconversion may not be reliably occur in severely immunocompromised patients.

Committee Discussion

The review was discussed by the Scientific Advisory Group on Dec 16, 2020 and March 19, 2021 (after additional Alberta-specific analyses were completed). It was suggested that the recommendations for isolation be aligned with CDC recommendations, namely 14 days for those with severe disease. It was further suggested that isolation recommendations need to consider both severity of disease and level of immunosuppression, and differentiate critical illness and immunocompromise for risk of prolonged carriage of cultivatable virus.

The committee discussed the robustness of the findings that isolated sore throat or runny nose was associated with decreased likelihood for a positive COVID test in multiple multivariable models. Unfortunately, given that there was still a significant rate of positive COVID-19 test results with isolated sore throat/runny nose and a concern about unexplored evolution of symptoms after initial presentation and screening, that this negative association was not strong enough to change recommendations regarding the need for testing or quarantine pending resolution of symptoms and/or a negative result. The addition of the AB public health surveillance online screening data was consistent with these findings and highlighted the limitations of symptoms noted at presentation to capture true measures of these symptoms over the course of the illness.

Additionally, the poor performance of these isolated symptoms in infants and young children as well as the inability to adequately evaluate symptoms of ageusia or anosmia in this age group limits their utility in predicting risk of COVID-19. The committee discussed the utility of serology testing, as well as specific Ct values, to guide isolation requirements. It was concluded that the current state of the research evidence was not sufficient to make recommendations based on these parameters. A member suggested the addition of a Cochrane collaboration descriptive analysis for predictive symptoms as a resource (Struyf[18]) which was used as framing and background only as it did not meet the criteria for inclusion and did not allow comparison to the other studies used.

Recommendations

1. Adults and children presenting with any of the core COVID-19 symptoms (fever, cough, shortness of breath, sore throat, runny nose) should be screened prospectively for the presence of dys/anosmia or dys/ageusia as a strong indicator

of the likelihood for COVID-19. Those found to have these symptoms should be prioritized for RT-PCR testing and early isolation. If RT-PCR is negative continued isolation and a repeat test should be considered.
Rationale: While ILI symptoms are common and nonspecific, anosmia and ageusia are highly predictive of COVID-19 positivity on RT-PCR.

2. Given the high positive predictive value of the presence of dys/anosmia or dys/ageusia, these symptoms should be included as part of the core COVID-19 symptoms used for screening both children and adults in public and health care settings.
Rationale: While ILI symptoms are common and nonspecific, anosmia and ageusia are highly predictive of COVID-19 positivity on RT-PCR.

3. Current data, although variable, supports that immunocompetent symptomatic people who test positive for COVID-19 remain in isolation until resolution of the primary ILI symptoms and/or for at least 10 days for mild to moderate disease and for up to 14 days for patients with severe disease, e.g. requiring hospital admission for supplemental oxygen therapy. There is less data on duration of recovery of virus by culture in critical illness, and presently longer isolation (21 days) should be considered in patients who have required ICU admission for COVID-19 disease (see Practical Guidance). Severely immunocompromised individuals, e.g. those with recent stem cell transplant, chemotherapy or B cell depleting therapies, should be assessed case-by-case in consultation with Public Health (for outpatients), and Infectious Disease and or Infection Prevention and Control (for inpatients) as they may have prolonged transmissible SARS-CoV-2 carriage.[1,2]
Rationale: Both detection of viable virus and transmission have been found to be negligible after the time points noted and are not associated with specific residual symptoms which relate to more severe lung disease. Immunocompromised individuals have been variably found to carry cultivatable virus for extended periods (over 21 days) which would still pose some risk of transmission. There has not been published data on prolonged cultivatable virus shedding in solid organ transplant or high dose steroid immunosuppression. Therefore this question should be addressed on a case by case basis as knowledge evolves.

4. Given that RT-PCR positivity can persist without cultivatable virus for variable and extended periods despite resolution of ILI symptoms in immunocompetent individuals, repeat RT-PCR testing should not routinely be used to determine ongoing isolation status or the ability to move back into a community setting.
Rationale: RT-PCR positivity alone does not suggest infectivity or transmission risk.

Practical Guidance

1. Although the risk of COVID-19 is lower in people with isolated sore throat and / or rhinorrhea, it remains significant and symptoms may continue to evolve across a variable time period, meaning that **individuals with these isolated symptoms should continue to isolate until symptoms resolve and get COVID-19 testing when feasible**.

Rationale: Multiple adjusted analyses suggest that the presence of an isolated sore throat or rhinorrhea are associated with a lower risk of COVID-19. In a study of 592 community Health Care Workers presenting with symptoms and or exposure to COVID-19, none of the workers presenting with isolated sore throat or nasal symptoms tested positive by RT-PCR test. In an AB Public Health Surveillance database of over 52,000 persons screened for COVID-19, isolated sore throat, isolated runny nose, or runny nose with sore throat and no other symptoms was associated with a low OR of 0.36 but a 4.2% rate for a positive COVID-19 RT-PCR. In a subgroup sample of the Alberta public health surveillance data including children, 0 to 5 years of age (n=1871), carried an OR > 1.5 for a positive COVID-19 test after screening positive for isolated runny nose or sore throat.
In a subgroup sample of 3657 of these Albertans with isolated sore throat and or runny nose for whom an RPP was available, the RPP was found to be positive around three times as often as a COVID-19 RT-PCR (15.6 vs 5.6%).

2. Given the lack of high quality studies examining long term clinical and laboratory testing follow up of residual symptoms after patients have tested negative for COVID-19 via RT-PCR, fully evidence-based recommendations on the duration of quarantine based on aspects of symptom duration and RT-PCR test results cannot be made. RT-PCR positivity temporally extends beyond the ability to cultivate live virus. In most cases, approximately four days after symptom onset, the ability to culture live virus declines and, by day 10, live virus is usually not detectable but RT-PCR test results are typically still positive. This suggests that **repeat RT-PCR should NOT be performed on COVID-19 positive individuals within 90 days of a positive test as residual viral shedding may result in RT-PCR positivity in the absence of transmission risk**, unless:
    a) New symptoms and exposures suggest the need to assess for reinfection if 6 weeks or longer after the initial symptom onset (refer to SAG reinfection review), or
    b) Severe immunocompromise (eg hematopoetic transplant, active chemotherapy or B cell depletion) and persistent clinical findings raise the possibility of persistent or recurrent infection.

3. A longer duration of recovery of cultivatable virus (to 20 days) has been reported in one study of patients with COVID-19 related severe and critical illness, some of whom had immunocompromise. In patient requiring critical care unit admission for COVID-19 disease, Infection Prevention and Control currently recommends isolation for 21 days from symptom onset. Policies may be revised with emerging data.

Research Gaps

1. Studies of symptoms noted at onset of illness as taken from assessment centres and online screening are not likely to reliably capture evolution of symptoms which may occur and necessary to identify symptoms that best predict a positive or negative COVID-19 RT-PCR test. In particular, identifying a way to reliably evaluate symptoms in infants and young children are required. Further study of Workplace

Health and Safety data with repeated interview of HCW may provide more robust symptom screening information going forward.

2. It is uncertain whether the symptoms present in patients with VOCs will be the same, and studies suggest that vaccinated patients may have milder symptoms. Changes to presentation in the context of VOC and in vaccinated individuals will need to be evaluated in future research on the epidemiology of symptoms of COVID-19 infections.

3. Studies included in this review reported significant variability in the duration of symptoms and duration of virus detectability by RT-PCR. Several factors may contribute to this substantial variability, and addressing these would enhance the quality of literature on this topic.

    a. Further delineation of demographic and clinical variables that may influence symptom or virus detectability duration (such as immunocompromised status, age, comorbidities, severity of present illness and constellation of COVID-19 symptoms) would be of value. Studies included in this review reported descriptive statistics (counts and proportions) of various demographic or clinical variables of potential significance. However outcome measures were rarely reported by these subgroups of clinical relevance. At the time of this review, there are insufficient descriptions of data within individual studies to warrant combining data from various studies, given the small number of comparable parameter outcomes.

    b. Although all included papers used “onset of symptoms” as an anchoring date, it is unclear if that term was defined consistently across all studies. For example, for hospitalized patient studies, onset of symptoms could be a patient-reported measure which includes onset prior to hospital admission. In other studies, hospital admission may have been used as the proxy for onset of symptoms. A common definition of “onset of symptoms” across various study types would assist comparability and improve data quality.

    c. Duration of follow-up was often limited - the true duration of mild, less severe symptoms after a negative COVID-19 test result and hospital discharge remain unclear. In addition, at the time of this review, there were no published studies which collected long term symptom data among patients who converted from a positive to a negative COVID-19 RT-PCR test result. Clinical improvement warranting discharge is unlikely to be equivalent with complete resolution of all symptoms.

4. Laboratory testing parameters which may influence virus detectability by RT-PCR are inconsistently reported (for example, cycle threshold values and cut off in use, and test manufacturer). RT-PCR tests are not validated as a quantitative test and

are not comparable between instruments and labs. While there is a trend that higher Ct values above 30 (testing platform specific) are correlated with a lower likelihood of detecting viable virus, these data are inconsistent and platform dependent. Considering that Ct values and thresholds vary across platforms, at this time repeat RT-PCR, and utilization of RT-PCR Ct to guide infectivity and discontinuation of isolation, cannot be made with certainty from the literature.

5. Transmission of viable virus is extremely unlikely when SARS-CoV-2 RT-PCR is truly negative. However, further research needs to be conducted among patients with longer term, residual symptoms with particular attention to those patients who are immunocompromised. Viral shedding in these specific patients may be longer and, as such, require prolonged infection prevention measures

6. Additionally, at this time, serologic testing remains non-routine at most public health laboratories; linkage between the development of IgG and reduced infectiousness is suggested but still debated in the literature. At this time there is insufficient literature to support use of serologic data as an indicator of communicability, nor as a tool to assist in the discontinuation of isolation.

7. Finally, the treatment that patients receive could feasibly influence symptom duration and detectability of virus, and therefore treatment data should be collected in symptom studies. A variety of therapies are under evaluation for COVID-19 with both virologic and immunologic modes of action. Understandably, variation in treatment decisions may exist across institutions and geographic areas. Patient outcome reporting would be strengthened and more comparable if treatment protocols administered to the study population were reported.

Strength of Evidence

The studies included in this review summarizing typical COVID-19 symptom time course and RT-PCR detectable virus over time were selected based on the reported duration from onset of symptoms (rather than date of first positive RT-PCR test or hospital admission/healthcare facility presentation) to reported clinical resolution (to determine symptom time course) or to first of two negative consecutive RT-PCR test results (to determine virus detectability). Further, only those studies which used respiratory samples for RT-PCR testing were included. Limiting studies to these parameters was done to ensure inclusion of equivalent studies in this review.

For those studies that included patients admitted to hospital, date of hospital discharge was commonly used as the last point of follow up. These studies typically reported that patients were discharged when COVID tests were negative combined with clinical improvement warranting discharge from acute care. Further, the majority of studies combined all symptoms together, rather than examining individual symptoms of interest. Clinical improvement warranting discharge may not be equivalent with complete resolution of all symptoms.

Research design, sample size and type of publication are summarized in Tables 1 and 2 for each study included in this review.

Summary of Evidence

1. What symptoms are predictive of a positive COVID-19 test in children and adults?

Fifteen studies (n=15), summarized in Table 1, analyzed symptoms predictive of a positive COVID-19 test via RT-PCR.[3-16] All but one[3] report on patients cared for in the community. One study specifically limited the study population to children.[9] Studies included in this review were limited to those that reported on population-based results from Alberta, Canada, were a Cochrane Library review, or presented a developed predictive model (rather than simple descriptive or univariate analyses).

King et al. reported on the symptoms that are associated with a positive COVID-19 test result in children, derived from population-based testing in Alberta, Canada.[9] The authors report that, among the children included in the Alberta sample, up to one third had no symptoms recorded in a database of Public Health follow-up despite testing positive for COVID. However, among those children with symptoms, altered taste or smell, nausea/vomiting or headache are predictive of a positive COVID test result. Combining all of these symptoms results in a positive likelihood ratio of 65.92 (95%CI 49.5-91.9) for a positive RT-PCR test derived from a respiratory sample (nasal, nasopharyngeal, or pharyngeal swab).

The same group used Alberta, Canada based COVID testing results and a Public Health database to analyze the symptoms most likely to predict a positive COVID RT-PCR test among adults.[13] In their study, the symptoms of anosmia/ageusia and decreased appetite were much more likely to be associated with a positive test compared to other symptoms such as malaise, joint pain, fever/chills, and headache.

Several other international studies of patients cared for in the community are aligned with Alberta results related to anosmia and ageusia as strong predictors for a positive COVID test result.[4-8,10-12,14,15,17] The quality of the predictive models included in Table 1 are low, due to lack of external validation and other methodological shortcomings. However, the frequency with which anosmia and ageusia appear as strong predictors for a positive COVID test result suggest that these two symptoms may serve as useful indicators for early detection of COVID-19. Fever,[4-6,11-17] headache[9,10,13] and cough[3,4,6,12,14] are also commonly reported as symptoms associated with COVID-19 test positivity in multiple models. Sore throat was often included in the models. Interestingly, when it was a statistically significant independent predictor in four studies, presence of this symptom was inversely associated with a positive COVID test result.[8,10,12,15]
A study of 592 community health care workers in Massachusetts identified that isolated rhinorrhea or sore throat was found in 6.7% of individuals presenting with symptoms or exposure to COVID-19. None of these cases were associated with a positive RT-PCR test result or development of additional symptoms or positive testing.[73]

A recent review of Alberta Public Health surveillance data from October 2020 to March 2021 identified 52,641 patients with isolated sore throat and/or runny nose out of 446, 528 patients with online screening data and COVID-19 RT-PCR results. This showed and OR of 0.36 for a positive COVID-19 RT-PCR test relative to those who screened

positive for other symptoms and /or exposure history (Table 2). When broken down by age, the presence of isolated runny nose and/or sore throat identified a declining OR for a positive COVID-19 RT-PCR by age with particularly poor performance in the 0-5 age group. (Table 3)

Additional data from 322 patients with isolated symptoms of sore throat and/or runny nose out of 3657 patients screened for both COVID-19 and a Respiratory Pathogen Panel (RPP), showed a much higher OR of 1.13 for a positive RPP than for a positive COVID-19 RT-PCR, at 0.30 (Table 4).

Table 1. Symptoms that are predictive for a positive COVID-19 test.

Publication	Predictive Symptoms	Model Performance	Population Description
King[9]	Anosmia/ageusia Nausea/vomiting Headache All three symptoms combined	Adj PLR 6.25 (95%CI 3.7-34.4) Adj PLR 4.86 (95%CI 2.4-18.8) Adj PLR 2.17 (1.8-3.8) Adj PLR 65.92 (95%CI 49.5-91.9)	Community Alberta, Canada Children only Mean age + = 9.3 (SD 5.2) Mean age - = 8.5 (SD 5.3) N=2463 (1987 positive) Population-based testing with concomitant patient/parent self-report of symptoms using standardized data collection. Other model variables: age, sex, inappetence, sneezing, muscle/joint pain, fever, malaise, nasal congestion, fatigue, dyspnea, sore throat, diarrhea, cough, rhinorrhea, chest pain, conjunctivitis. No external validation
McAlister[13]	Anosmia/ageusia Decrease appetite Diarrhea Nausea/vomiting Malaise Muscle/joint pain Sneezing Fever/chills Headache	PLR 10.4 (95%CI 8.1-13.2) PLR 4.9 (95%CI 3.2-5.1) PLR 2.7 (95%CI 2.2-3.2) PLR 2.7 (95%CI 2.2-3.2) PLR 2.2 (95%CI 2.0-2.5) PLR 1.8 (95%CI 1.6-2.0) PLR 1.8 (95%CI 1.5-2.2) PLR 2.0 (95%CI 1.9-2.2) PLR 2.0 (95%CI 1.9-2.2)	Community Alberta, Canada N= 15132 (11702 positive) Population-based testing with concomitant patient self-report of symptoms using standardized data collection.
Ahamad[3]	Lung infection Cough Runny nose Pneumonia Muscle soreness Diarrhea	0-20 years: AUC 0.85 21-60 years: AUC 0.87 61-96 years: AUC 0.82 0-96 years: AUC 0.85	Hospital patients China Median age 43 (IQR 32-55) N=6512 (1572 positive) Machine learning model Training (70%) and testing (30%) Results for XGBoost algorithm Other model variables: age, gender, travel history, isolation treatment No external validation
Allen[4]	Loss of taste/smell Fever	OR 33.2 (95%CI 17.3-67.9) OR 6.3 (95%CI 2.8-13.7)	Community USA Mean age 42 (SD 16.3) N=3514 (315 positive)

	Cough	OR 4.5 (95%CI 2.8-7.0)	Patient self-report through web and mobile phone application Other model variables: age, race, income, population density, comorbidities, other symptoms, exposure history No validation
Clemency[5]	Any one or more of the following symptoms: Fever Loss of taste Loss of smell	Sen = 0.89 (95% CI 0.85-0.93) Spec = 0.48 (95%CI 0.44-0.52) PPV = 0.34 (0.31-0.38) NPV = 0.93 (0.91-0.96) AUC=0.75	Healthcare workers USA N=961 (225 positive) Standardized list of symptoms Model= any one or more of three symptoms listed No validation
Dixon[6] Pre-print	Fever Anosmia Ageusia Cough	OR 5.3 OR 4.1 OR 2.4 OR 2.9 AUC = 0.91	Community USA Age: 12 years and older N=8214 (368 positive) Patient self-report using standardized checklist Other model variables: shortness of breath, chest pain, muscle ache, fatigue, headache, diarrhea, vomiting, sore throat, runny nose, age, sex, race, urban/rural. No validation
Gerkin[7] Pre-print	Change in smell Change in taste	AUC 0.71	Community International Age >19 years N= 15747 (8273 positive) Patient self-report through an online survey (32 languages) Other model variables: sore throat, nasal obstruction,
Just[8] Pre-print	Anosmia Sore throat	OR 4.54 (95% CI 1.51-13.67) OR 0.33 (95% CI 0.11-0.97)	Primary care patients Germany Median age=44 (IQR 31-59) N=374 (40 positive) Structured data collection form Other model variables: age, chills, +/- symptoms of first grade contact No validation
La Torre[10]	Anosmia Ageusia Headache Sore throat	OR 14.75 (95%CI 4.3-50.9) OR 9.18 (95%CI 2.8-30.2) OR 3.92 (95% CI1.5-10.6) OR 0.05 (95% CI 0.01-0.41)	Healthcare workers Italy Mean age: 43.6(12.9) controls; 40.7 (12.9) cases N=105 (30 positive) Structured interview conducted by physicians Other model variables: fever, cough, asthenia, myalgia, diarrhea, thoracic pain, conjunctivitis, rhinitis. No validation

Lan[11]	Fever Myalgia Nasal symptoms Anosmia/ageusia	OR 2.9 (95%CI 1.7-5.0) OR 1.8 (95%CI 1.0-6.2) OR 0.4 (95%CI 0.2-0.7) OR 7.2 (95%CI 3.0-17.7)	Healthcare workers USA Mean age= 43.6 (SD 12.9) N=592 (83 positive) Self-report on a standardized data collection form Nasal symptoms = runny, sneezing, congestion Other model variables: malaise, shortness of breath, GI symptoms, headache No validation
Lombardi[12]	Taste/smell change Fever Dyspnea Asthenia Myalgia Cough Sore throat	OR 51.4 (95%CI 17.6-150) OR 9.1 (95%CI 5.6-14.8) OR 5.8 (95%CI 2.4-14.0) OR 3.7 (95%CI 1.7-7.9) OR 2.2 (95%CI 1.0-4.6) OR 1.7 (95%CI 1.1-2.8) OR 0.3 (95%CI 0.1-0.6)	Healthcare workers Italy Mean age=44.5 N=1573 (139 positive) Other model variables: coryza, headache, GI symptoms, ocular symptoms, No validation
Menni[14] Pre-print	Taste/smell loss Fever Cough Fatigue Diarrhea Abdominal pain Inappetence	AUC = 0.77 (0.72-0.82; test) AUC = 0.75 (0.72-0.77; cross-validation)	Community UK general population N=1702 (579 positive) Patient self-report through an app Age: 16-90 years; mean=41
Roland[15]	Smell or taste change Body aches Fever/chills Sore throat Shortness of breath	OR 7.4 (95%CI 3.7-14.8) OR 3.1 (95%CI 1.4-7.0) OR 2.4 (95%CI 1.1-5.0) OR 0.3 (95%CI 0.2-0.6) OR 0.2 (95%CI 0.1-0.4) AUC 0.82	Community USA N=302 (145 positive) Patient self-report through an online survey advertised through social media Mean age=39
Smith[17]	Loss of smell or taste (2 points) Fever and cough (1 point) Wheeze or chest tightness (-1 point) “C19 Rule”	Score of 3: Likelihood ratio 15.0 (95%CI 2.0-112) Score of 2: LR 42.0 (95%CI 1.9-9.1) Score of 1: LR 1.2 (95%CI 0.7-1.9) Score of -1: LR 0.1 (95%CI 0.02-0.4) AUC=0.74	Community USA N=240 (120 positive) Patient self-report through telephone consultation using standardized data collection form Median age=43 (range 20-88) No external validation
Zavaski[16] Pre-print	Fever Dyspnea Coryza Fatigue	OR 4.0 (95%CI 2.3-7.1) OR 1.8 (95%CI 1.1-3.1) OR 0.4 (95%CI 0.2-0.8) OR 2.1 (95%CI 1.1-3.9) AUC Development: 0.80 (0.76-0.86) AUC Validation 0.88 (081-0.96)	Community Brazil N=464 (98 positive) ED presentations; data collected from medical records Mean age=48 Other model variable: Age≥60 No external validation

Adj PLR = adjusted positive likelihood ratio, AUC=area under the curve, CI=confidence interval, ED=emergency department, IQR=interquartile range, LR=likelihood ratio, NPV=negative predictive value, OR=odds ratio, PPV=positive predictive value, Sen=sensitivity, Spec=specificity.

Alberta data from Public Health Surveillance & Reporting: Analysis of COVID-19 test results in Albertan patients with sore throat, runny nose, or both without any other noted symptoms

This analysis is based on the online screening tool symptom data, therefore is self reported at the time of online test booking so may better reflect dominant early symptoms versus than post testing symptom survey based data.
In these data, 4.2% of individuals, (OR 0.36), with isolated sore throat and/or runny nose as initial symptoms tested COVID positive. Subsequent symptoms were not assessed so whether these individuals progressed to develop more symptoms after test booking is unknown and findings by age showed a decreasing OR by age (table 3).

Table 2 Isolated Symptoms and likelihood of a positive COVID-19 RT-PCR in AB Public Health Online Screening Data:

Isolated Symptoms* Type	Total reporting symptoms	COVID Positive	COVID Negative	Positive rate per symptoms	Odds Ratio	Lower CL	Upper CL
Runny Nose only	14,340	709	13,631	4.94%	0.46	0.42	0.49
Sore Throat only	29,850	1,228	28,622	4.11%	0.37	0.35	0.39
Runny Nose and Sore Throat Only	8,451	272	8,179	3.22%	0.29	0.26	0.33

*Among n=446,528 online screening records with COVID symptoms data that matched to a COVID test:

- 401,619 (89.94%) resulted in a negative COVID test.
- 44,909 (10.06%) tested positive for COVID.

Data Notes:

- Only positive and negative COVID test results with a valid ULI match to an online screening record with symptoms reported are included in this analysis.
- Analysis does not account for persons who received multiple/repeat swabs on the same day.
- Data as of Mar 5, 2021

Table 3 Isolated Symptoms of Runny Nose and/or Sore Throat by Age and likelihood of COVID-19 RT-PCR in AB Public Health Online Screening data:

a)

RUNNY NOSE ONLY by Age Group	Total reporting symptoms	COVID Positive	COVID Negative	Positive rate per symptoms	Odds Ratio	Lower CL	Upper CL
0-5 years	1,649	76	1573	4.61%	1.51	0.19	1.93
6-11 years	909	31	878	3.41%	0.79	0.55	1.13
12-17 years	722	39	683	5.40%	0.66	0.48	0.92
18-64 years	10,866	566	10,300	5.21%	0.44	0.4	0.48
65+ years	932	30	902	3.22%	0.26	0.18	0.38

b)

SORE THROAT ONLY by Age Group	Total reporting symptoms	COVID Positive	COVID Negative	Positive rate per symptoms	Odds Ratio	Lower CL	Upper CL
0-5 years	222	14	208	6.31%	2.07	1.2	3.57
6-11 years	1,548	65	1,483	4.20%	0.98	0.76	1.26
12-17 years	1,953	93	1,860	4.76%	0.57	0.46	0.7
18-64 years	26,861	1,080	25,781	4.02%	0.32	0.3	0.34
65+ years	1,278	42	1,236	3.29%	0.27	0.19	0.36

c)

RUNNY NOSE AND SORE THROAT ONLY by Age Group	Total reporting symptoms	COVID Positive	COVID Negative	Positive rate per symptoms	Odds Ratio	Lower CL	Upper CL
0-5 years	243	5	238	2.06%	0.64	0.26	1.55
6-11 years	606	15	591	2.48%	0.56	0.34	0.94
12-17 years	591	16	575	2.71%	0.32	0.2	0.53
18-64 years	7,156	241	6,915	3.37%	0.28	0.25	0.32
65+ years	450	12	438	2.67%	0.22	0.12	0.39

Although a somewhat different population, the same analysis of those with respiratory pathogen panel, (RPP), findings were requested. It is noted that RPP tests in addition to COVID tests are ordinarily ordered by physicians in other care settings, (acute care and facilities), rather than at COVID-19 Assessment centres so these data are limited in number (n=3657 that had symptom data, and RPP and a COVID test.) Of those, 72% had a negative test, 15% had a positive COVID test, and 13% had a positive RPP, with 0.61% testing positive for both. In this cohort, isolated symptoms of runny nose and/or sore throat were more strongly associated with a positive RPP (15.8% vs 5.6%) with an OR of 1.13 vs 0.30 for a positive RPP vs a positive COVID-19 RT-PCR.

Table 4 Isolated Symptoms of Runny Nose and /or sore throat and likelihood of a positive COVID-19 RT-PCR vs Respiratory Pathogen Panel (RPP) in a sample of 322 patients from AB Public Health Surveillance data

a) COVID:

Isolated Symptoms Type	Total reporting symptoms	COVID Positive	COVID Negative	Positive rate per symptoms	Odds Ratio	Lower CL	Upper CL
RUNNY_NOSE_ONLY	92	5	87	5.43%	0.32	0.13	0.8
SORE_THROAT_ONLY	178	12	166	6.74%	0.40	0.22	0.73
RUNNY_NOSE_AND_SORE_THROAT_ONLY	52	1	51	1.92%	0.11	0.15	0.80

b) RPP

Isolated Symptoms Type	Total reporting symptoms	RPP Positive	RPP Negative	Positive rate per symptoms	Odds Ratio	Lower CL	Upper CL
RUNNY_NOSE_ONLY	92	13	79	14.13%	1.06	0.58	1.91
SORE_THROAT_ONLY	178	23	155	12.92%	0.95	0.61	1.48
RUNNY_NOSE_AND_SORE_THROAT_ONLY	52	15	37	28.85%	2.65	1.44	4.86

*Among n=3657 online screening records with COVID symptoms data that matched to a COVID and an RPP test:

Data Notes:

- Only positive and negative Respiratory Pathogen Panel test results with a valid ULI match to an online screening record with symptoms reported are included in this analysis.
- Only Respiratory Panel results exceeding the COVID screening record are included in analysis.
- Data as of Mar 18, 2021

2. What is the typical time course of COVID-19 symptoms?

Fourteen studies (n=14) were eligible for inclusion to summarize the duration symptoms among patients with COVID-19.[19-32] Table 2 provides a summary of key elements for each study including research design, patient population description, number of patients, and list of recorded symptoms (when reported). Mean or median, and associated measures of variability, for days to clinical resolution of symptoms are presented. Included studies reported symptom onset and resolution through patient self-report,[24,29,30] chart review[20-22,25,26,31,32] or prospective data collection by healthcare professionals.[19,23,27,28] Where sufficient data were provided to perform a transposing calculation, medians were converted to means.[33,34] This allowed for graphical comparison of study results; this comparison is presented in Figure 1. One additional paper focused on prospective follow-up of patients with olfactory and gustatory disorders, following 357 patients with anosmia, which suggested that 72.6% of these patients recovered olfactory function within the first 8 days following the resolution of the disease, although the methods and definitions in this study did not allow inclusion in the table.[68]

Individual Symptoms – Adult Community Patients

Three studies reported the duration of individual symptoms.[24,27,30] These studies included adult patients who were cared for in the community setting and one specifically focused on symptoms among healthcare workers. In all three studies, fever was a symptom with a shorter duration (~6 days), while diminished sense of smell represented a symptom of longer duration (~2 weeks). Six symptoms were similarly reported across the three studies. Their pooled mean (SD) number of days to clinical resolution are presented below:

Fever = 5.9 (6.4)
Headache = 8.1 (7.6)
Body Aches = 8.2 (7.5)
Cough = 13 (11.1)

Diminished Taste = 13.6 (12.0)
Diminished Smell = 14.2 (12.7)

Fever – Hospital Patients

Time to fever resolution among adult patients treated in hospital was specifically reported in four (n=4) studies.[21,28,31,32] The median time ranged from 4 to 12 days. Fever resolution among children admitted to hospital was reported as a mean of 3 days in one study.[26]

Grouped Symptoms

Eight (n=8) studies described COVID-19 symptom duration by considering a collection of symptoms.[19,20,22-24,28,29,31] When reported, the specific symptoms considered as a collection for each study are listed in Table 2.

Combined symptom duration for adult patients treated in the community was reported in three studies.[19,24,29] Two studies report the same median duration, namely 5 days (IQR 3-11) while a longer duration is calculated in the remaining study (mean=11.6 days).

Four studies reported the combined symptom duration for adult patients admitted to hospital.[20,22,28,31] Median symptom duration ranged from 8 days[20] to 27.5 days,[22] while two studies reported similar duration of 12 & 13 days.[28,31] The severity of illness was not reported in the study with the shortest duration, while the study with the longest duration included patients with moderate to severe illness. The two studies reporting similar duration of approximately 12 days included patients considered to have mild to moderate severity of illness.

Children (n=71 patients ranging in age from 0.07 years to 18 years) had a median duration of symptoms of 11 days (IQR 1-36).[23]

3. How are symptoms related to SARS-CoV-2 RT-PCR positivity and cultivatable virus over time?

Thirty-one studies (n=31) were eligible for inclusion to summarize the duration of virus detectability by RT-PCR among patients with COVID-19 relative to the onset of their symptoms.[19-23,26,28,30-32,35-55] For all included studies, time to laboratory resolution was defined as the duration between symptom onset and the first of two negative consecutive RT-PCR COVID-19 tests. Selected studies were limited to those that utilized respiratory samples (oropharyngeal swabs, nasopharyngeal swabs, sputum samples or bronchoalveolar lavage samples) for RT-PCR testing.

A summary of key elements for each study including research design, patient population description, number of patients, and list of recorded symptoms (when reported) is presented in Table 2. Mean or median, and associated measures of variability, for days to laboratory resolution, as defined by RT-PCR negative test results, are presented. Where sufficient data were provided to perform a transposing calculation, medians were converted to means.[33,34] This allowed for graphical comparison of study results and the comparison is presented in Figure 1.

RT-PCR Virus Detectability Duration by Individual Symptoms

Talmy et al. reported duration of RT-PCR positivity by various symptoms in a population of young patients with mild illness who were cared for in a COVID quarantine centre.[49] Considering all patients and all symptoms, the virus was detectable by RT-PCR for

three weeks (median = 21 days (IQR 15-27)). Shorter detectability durations were reported among patients with presenting symptoms of chills or dyspnea (median of 14 and 15 days respectively), while patients with symptoms of abdominal pain and nausea had longer RT-PCR positivity durations (median of 25 and 26 days).

RT-PCR Positivity Duration from Onset of Unspecified, Grouped Symptoms Among Patients Admitted to Hospital

Duration of RT-PCR positivity by RT-PCR among adult patients who were admitted to hospital substantially varied across published reports. Buetti et al. and Zhou et al. assessed severe patients only and reported median durations of 29 days and 31 days respectively.[35,55] Seven (n=7) studies included a mix of adult patients with reported mild, moderate and severe disease.[22,31,32,42,48,52,54] The shortest reported median duration in these studies was 12 days[31]. Three studies (n=3) reported a median duration of 17 days[42,48,54] and a further three studies (n=3) reported median durations ranging from 20 to 38 days.[22,32,52] In studies for which disease severity was not reported, the median duration of RT-PCR positivity among adult patients admitted to hospital ranged from 8 days to 19 days. Han et al. documented the longest average duration of detectability among adult patients admitted to hospital, namely a mean of 38.1 days. The authors indicated that their study population included patients with mild disease only. “Severity” was defined variously among the trials but admission to hospital and need for supplemental oxygen are suggested as common criteria.[59]

Four studies (n=4) reported on the mean or median duration of RT-PCR positivity by RT-PCR among children cared for in hospitals and community quarantine facilities. The reported mean/median durations were 6.4 days (severity not specified),[26] 11.1 days (mild and moderate severity),[53] 17 days (mild severity),[45] 18.7 days for upper respiratory tract symptoms (mild, moderate and severe),[23] and 19.9 days for lower respiratory tract symptoms (mild, moderate and severe).[23]

RT-PCR Positivity Duration from Onset of Unspecified, Grouped Symptoms Among Patients Cared for in the Community Setting

A similar variation in reported mean/median duration of RT-PCR positivity from onset of symptoms was reported among patients cared for in the community setting. Omar et al. reported a median duration of 20 days among patients in home isolation.[47] Cariani et al. and Romao et al. also assessed home isolation patients where the study population was comprised of healthcare workers.[30,37] Reported durations for these studies were 28 days[37] and 31 days.[30]

Studies Assessing both Symptom and RT-PCR or Viral Culture Positivity Duration in the Same Study Population

Ten studies (n=10) assessed the time from symptom onset to clinical resolution and laboratory resolution (time to negative RT-PCR test result) within the same population of patients.[19-23,26,28,30-32] Six studies (N=6) considered all symptoms collectively,[19,20,22,26,28,31] while four studies (n=4) highlighted specific individual symptoms. The calculated mean time from onset of symptoms to clinical resolution ranged from 3 to 25.7 days, while time from symptom onset to laboratory resolution ranged from 6.4 to 40.1 days (see Figure 1).[21,23,30,32] With the exception of one study,[31]

all authors reported that clinical resolution of symptoms occurred before a negative RT-PCR test result was achieved.

With respect to detection of viable virus by culture, three studies[56-58] found no cultivatable virus after day 8 (on days 9-20) post symptom onset, suggesting persistent RT-PCR positivity of nonviable virus. A review by Walsh et al., examined thirteen studies in which five studies found no cultivatable virus after day 10 of symptom onset.[59] The remaining eight studies had a limited number of cases. In two of these, a total of 3 of 186 (1.6%) RT-PCR samples collected from day 10-14 after onset were culture positive. Two case reports and four case series, with a combined total of 436 samples, demonstrated a fraction (1 sample at day 20 (1/129), 1 sample at day 32 (1/49) of samples had cultivatable virus on days 15-32, with a single study describing a virus culture positive on day 67 since symptom onset.[59] A targeted literature search around immunocompromised status and duration of viral detection yielded two additional reports. In a case study, a patient on cyclophosphamide, intermittent rituximab and eculizumab for antiphospholipid antibody syndrome was found to have persistent infection with recurrent low CT values, although culture was not performed but phylogenetic analysis was consistent with persistent infection and accelerated viral evolution[69]. In addition a case series of virologic studies on 20 severely immunocompromised patients with (18 hematopoetic stem cell transplant/chimeric antigen receptor (CAR) t cell therapy recipients and 2 lymphoma patients) with COVID-19 assessed RT-PCT and viral culture was identified. Eleven of the patients had severe disease, and 15 were on chemotherapy. Viral culture was positive in the first sample of 10/14 nasopharyngeal samples, and 3 patients had positive cultures for 8 to 21 days and 3 were culture positive for > 21 days (25, 26 and 61 days) after symptom onset. The latter three patients had stem cell or T cell therapy within the prior 6 months and remained seronegative for viral nucleoprotein antibodies. Whole genome sequencing supported that these represented persistent infection[70]. Finally, a review of solid organ transplant patients with COVID-19 identified 62 studies that documented viral shedding by PCR (none used culture), in which the majority of the series showed patients became RT-PCR negative at 3-5 weeks from the initial positive result (range 5-56 days.) In this review most of the patients had severe disease, with 81% of 2772 patients required hospital admission and the overall mortality was 18.65[71]. In a study[74] that included an assessment of immunosuppression, shorter duration of illness, and higher viral load were associated with positive culture, but the presence of immunosuppression was not significantly associated on univariate or multivariate analysis. Severe or critical COVID patients were included and the median time of shedding infectious virus was 8 days after symptom onset (IQR 5-11, range 0-10) shedding of infectious virus was common after 8 days of symptoms, and the likelihood of finding infectious virus was <5% if neutralizing antibody was present at a titer of >1:80.

Variation in Study Outcome Measures

Studies included in this review were selected based on the reported duration from onset of symptoms to reported clinical resolution (to determine symptom time course) and to first of two negative consecutive RT-PCR test results (to determine RT-PCR positivity). Further, selected studies were limited to those that utilized respiratory samples for RT-PCR testing. Figure 1 graphically demonstrates the variation in outcome measures

across selected studies. Table 2 summarizes the collection of symptoms that were included to assess clinical resolution.

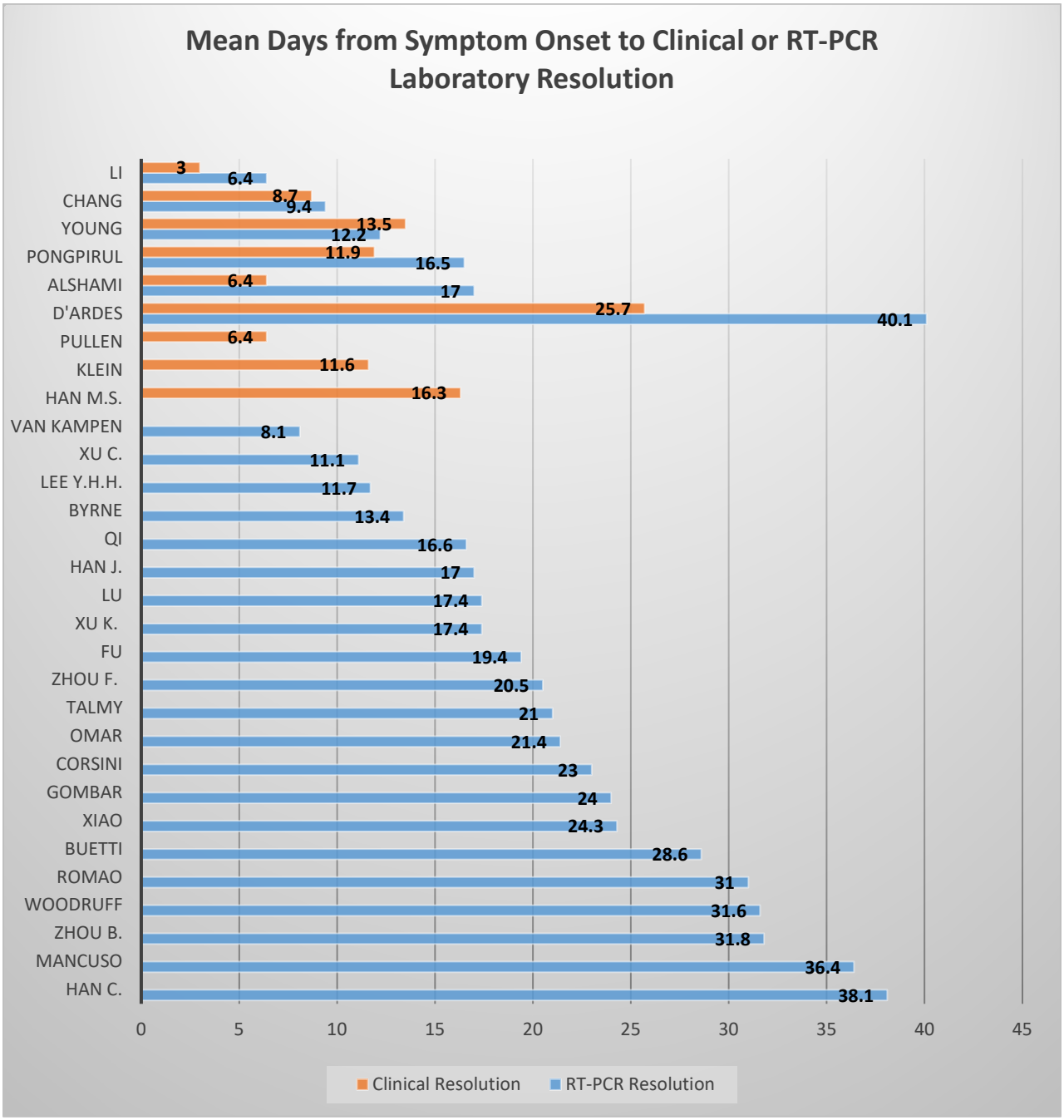

Figure 1. Mean number of days from symptom onset to clinical resolution (variously defined) or laboratory resolution (time to first of two consecutive negative RT-PCR tests). Where medians and minimum/maximum range or interquartile range were reported, this measure of central tendency was transposed to means and standard deviations to allow for visual comparison of study results [33,34].

Duration of Infectiousness – Comparing Duration of RT-PCR Positivity and Virus Culture

Interpretation of cycle threshold (Ct) values, as determined by RT-PCR, must be done with caution, as they do not directly reflect true viral loads. Rather they vary between platform/assay and require standardization using reference curves. Eleven (n=11) publications, including six (n=6) reviews[56-61] and five (n=5) original studies[62-66] were reviewed pertaining to Ct values and viral isolation/culturability, as a measure of infectivity. In general, a lower Ct value is representative of a higher concentration of viral RNA, and thus may represent a higher viral load in the sample collected, although importantly, sampling variability may impact results with inadequate samples more likely to have a high Ct/low viral load.[56] Of note, the review by Cevik et al.[56] found cultivatable virus and RT-PCR positivity was longer in immunocompromised than immunocompetent hosts. While the methods vary considerable between the studies compared, Cevik et al., suggests immunocompromised hosts should be considered infectious until day 21.

Seven studies (n=7)[57-59,61-64] reveal a trend where serial Ct values were lowest during the first 5-7 days of symptoms with the lowest Ct values on days 3 and 4 of symptoms.[62] When symptom onset is clearly known, a bimodal distribution can be expected for Ct values, where values are high in pre-symptomatic days (dependent upon platform/assay can exceed 30) then dropping to a trough on day 3-4 (dependent upon platform/assay often in teens to low 20s), and then slowly increasing. Salvatore's work, using either the QIAgen EZ1 Advanced XL or the bioMérieux EMAG, and RT-PCR ABI 7500 suggests a mean Ct value of 26.5 during the first seven days of symptoms, and contrasts this with a median Ct value of 35 at day 21.[63]

The second trend described in four (n=4) papers[61-64] suggests that likelihood of positive viral culture, and thus infectivity, decreases dramatically with Ct values above 24-34 in the various assays reported. Bullard et al., using Ambion AM1836 RNA kit (Thermo Fisher) paired with the Kingfisher Flex instrument (Thermo Fisher), on Bio-Rad CFX96 thermal cycler, suggest a decreasing OR of 0.64 (95% CI 0.49-0.84; $p<0.001$) for each Ct value, suggesting a 32% reduction in the likelihood of positive culture with an increase in 1 Ct.[62] Young et al. suggest that in their laboratory protocol, Ct values greater than 30 collected >14 days after symptom onset, did not result in viral isolation, and thus can be considered a non-infectious samples.[67]

One study identified 129 patients admitted to hospital for severe COVID-19 including 89 admitted to ICU who had at least one viral culture available in addition to symptoms, RT-PCR data as well as a subgroup with serological data. [50] 17.8% or 62 samples from 23 patients were found to be infectious. The median time of infectious virus shedding was 8 days post onset of symptoms (IQR 5–11, range 0–20) with less than ≤5% having for isolating infectious SARS-CoV-2 when the duration of symptoms was 15.2 days (95% CI 13.4–17.2) or more. The median viral load was significantly higher in culture positive samples than in culture negative samples (8.14 versus 5.88 Log10 RNA copies/mL, $p < 0.0001$) and the probability of isolating infectious SARS-CoV-2 was less than 5% when the viral load was below 6.63 Log10 RNA copies/mL (95% CI 6.24–6.91). For 27 patients, neutralizing antibody titers from 112 serum samples that were obtained

on the along with the respiratory tract sample. The probability of isolating infectious virus was less than 5% when the neutralizing antibody titer was 1:80 or higher.
A viral load exceeding 7 Log10 RNA copies/mL, less than 7 days of symptoms, absence of serum neutralizing antibodies and being immunocompromised were all associated with a positive virus culture in univariate analysis but only a viral load above 7 Log10 RNA copies/mL and absence of serum neutralizing antibodies were independently associated with isolation of infectious SARS-CoV-2 from the respiratory tracts of these 27 individuals. [50] A longer infectious period of up to 20 days was found in this more severely ill population which included a larger proportion of critical care patients and a number of immunocompromised patients. They suggested that infection prevention and control precautions should consider disease severity in these populations and not just symptom duration. They suggest use of viral load and/or the presence of neutralizing antibodies rather than duration of symptoms or RT-PCR Ct levels but availability of this testing is not currently felt to be viable or consistent.

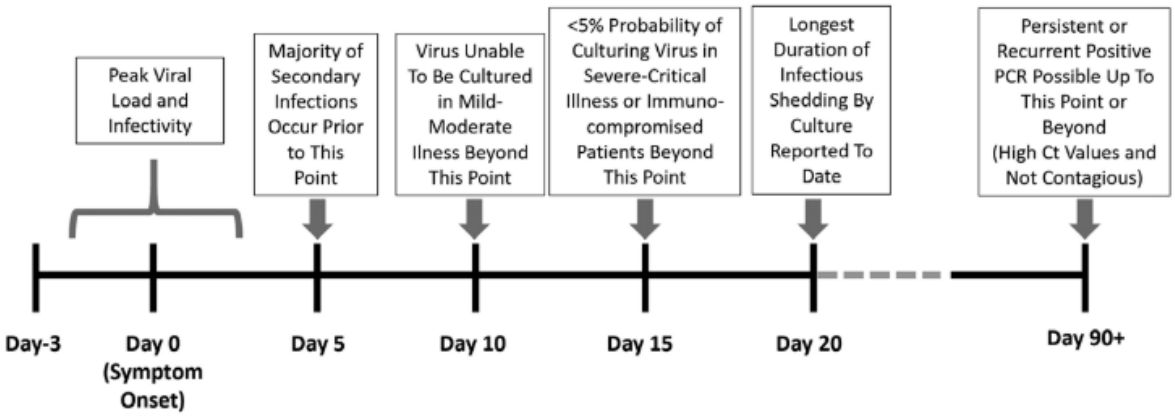

Figure 2. Summary of SARS-CoV-2 infectivity timeline. From: Rhee C. Kanjilal S., Baker M, Klompas M. Duration of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infectivity: When Is It Safe to Discontinue Isolation? Clinical Infectious Diseases, 2020, https://doi.org/10.1093/cid/ciaa1249

Table 2. Duration of COVID-19 symptoms and SARS-CoV-2 RT-PCR positivity

Publication	Clinical Resolution (Days)	Laboratory Resolution by RT-PCR (Days)	Study Population
Alshami[19] Prospective cohort Standardized data collection by HCW	Median = 5 (IQR 3-11)	Median = 17 (IQR 12.4-21.6)	N=128 patients Community - quarantine facility Low risk, stable patients Saudi Arabia Mean age = 39.6 years (range 8-76 years) Symptoms include fever, chills, muscle aches, sore throat, cough, SOB, nausea/vomiting, headache abdominal pain, diarrhea, loss of taste or smell.
Buetti[35] Prospective cohort Standardized data collection		Median = 29 (IQR 23-34)	N=90 Hospital patients ICU patients France & Switzerland Adults

			Median age = 62.5 (IQR 54-70)
Byrne [36] Scoping review with meta-analysis of means		Mean = 13.4 (95% CI 10.9-15.8)	N= 15 studies Severity not specified Adults and children Hospital and community patients
Cariani[37] Retrospective cohort		Median = 28 (variability not provided)	N=58 patients Healthcare workers Severity not specified Mean age = 42 years (SD 13.8) Italy Symptoms: fever, cough, headache, rhinitis, sore throat, muscle/joint pain, anosmia, ageusia, conjunctivitis, dyspnea, GI symptoms
Chang[20] Retrospective cohort Chart review Published letter	Median = 8 (IQR 6.3-11.5)	Median = 10.5 (IQR 6-12)	N=16 patients Hospital patients Severity not specified China Median age = 35.5 years (IQR 24-43) (range 3-68) Symptoms: fever, cough, sore throat, dyspnea, diarrhea, weakness, dizzy
Chen[21] Retrospective cohort Chart review	Median = 10 (95% CI 8-10) Fever only	Median = 11 (95% CI 10-12)	N= 249 patients Hospital patients (9% in ICU) Severity not specified China Median age = 51 years (IQR 36-64) Symptoms: fever, cough, fatigue, dizziness, headache, shortness of breath, rhinorrhea, sore throat, diarrhea and inappetence.
Corsini[38] Retrospective cohort Chart review		Median = 23 (IQR 17-29)	N=251 Hospital and ambulatory patients Severity not specified USA Adults Median age = 53 (IQR 40-66) Symptoms include: cough, dyspnea, fever, chills, shivering, muscle pain, diarrhea, headache, sore throat, ageusia, anosmia, dizziness.
D'Ardes[22] Retrospective cohort Chart review	Median = 27.5 (IQR 17-33)	Median = 38 (IQR 31.7-502)	N=73 patients Hospital patients Mild, moderate & severe Italy Median age = 63 years (IQR 52-76) Symptoms include cough, fever, and dyspnea.
Fu[39] Retrospective cohort Chart review		Median = 19 (IQR 16-23) (range 3-44)	N=410 Hospital patients Severity not reported China

Published letter			Median age=52 (IQR 38-66)
Gombar[40] Retrospective cohort		Mean = 24 (variability not provided)	N= 63 HCWs N= 87 Hospital patients Severity not specified Adults USA Patient mean age = 57.2 (21.7 SD) HCW mean age = 35.5 (SD 11.1)
Han C. [41] Retrospective cohort Chart review		Mean = 38.1 (range 15-62) Total cohort Mean = 40.9 (digestive only) Mean = 42.0 (digestive + resp) Mean = 33.5 (Resp only)	N=206 patients Hospital patients Mild severity China Mean age = 62.5 (range 27-92) Symptoms: N=48 digestive symptoms alone (poor appetite, vomiting, diarrhea, abdominal pain) N=69 digestive + respiratory symptoms (cough, chest distress, shortness of breath, sore throat) N=89 respiratory symptoms alone
Han J.[42] Retrospective cohort Chart review		Median = 17 (IQR 11-23) (range 4-51)	N=185 Hospital patients Mild, moderate & severe China Mean age=44 (SD 17.88)
Han M.S.[23] Prospective cohort Standardized data collection by HCW	Median = 11 (range 1-36)	Mean = 18.7 (SD 5.8) URTI Mean = 19.9 (SD 5.6) LRTI	N=71 patients Hospital patients and community quarantine facility Mild, moderate & severe Korea Children less than 19 years old Median age = 11 (range 0.07-18) Symptoms include fever, headache, myalgia, lethargy, chills, cough, sputum, rhinorrhea, sore throat, nasal congestion, chest discomfort, dyspnea, diarrhea, abdominal pain, nausea/vomiting, loss of taste, loss of smell, eye pain.
Klein[24] Prospective cohort Patient self-report via telephone survey Pre-print	Mean Fever 5.8 (SD 8.6) Appetite loss 7.8 (SD 6.9) Headache 7.8 (SD 8.5) Muscle aches 6.9 (SD 8.1) Dry cough 14.8 (SD 14.6) Taste change 17.2 (SD 17.6) Smell change 18.9 (SD 19.7)		N=112 patients Community, ambulatory patients Severity not specified Israel Adults Mean age = 35 (SD 12)
Klopfenstein[25] Retrospective cohort Chart review	Mean=8.9 (SD 6.3) (range 1-21) Anosmia only		N=54 Hospital and ambulatory patients Severity not specified France Adults Mean age=47 (SD 16)
Lee Y[43]		Median	N=488 patients

Prospective cohort Data collected by physicians through a telephone interview		Anosmia = 7 (variability not reported) Ageusia = 7 (variability not reported)	Community and some hospital patients Mild, moderate and severe Anosmia & ageusia = 254 Ageusia only = 99 Anosmia only = 135 Korea Adults Median age = 36.5 (range 24.5-54.0)
Lee YHH[44] Prospective cohort		Mean = 11.7 (SD 8.2) (Range 2-41)	N=242 Community treatment centres Mild Korea Adults (mean age for those with symptoms not provided) Symptoms include: dyspnea, cough, sputum, rhinorrhea, sore throat, diarrhea, dyspepsia, constipation, headache, fever.
Li[26] Retrospective cohort Chart review	Mean = 3.0 (SD 2.1) (range 1-8) Fever only	Mean = 6.4 (SD 2.9) (range 4-18)	N=40 Hospital patients Severity not specified China Children Mean age = 5.6 years (range 0.2-16.8)
Lu[45] Retrospective cohort Chart review		Median = 17 (IQR 12-23)	N=110 Hospital patients Mild China Children Median age = 6 (range 2 months-15 years)
Mancuso[46] Prospective cohort Population-based Standardized data collection and chart review		Median = 36 (IQR 28-45) Total Cohort Median = 38 (IQR 30-47) Hospital admissions Median=36 (IQR 29-47) ED use only Median=33 (IQR 25-41) No ED or hospital admission	N=1162 Hospital and community patients Severity not reported Italy Adults Mean age = 60.7 (±16.3)
O'Keefe[27] Retrospective cohort Standardized data collection by a HCW via telemedicine visits	Mean (95% CI) Fever 5.9 (5.1-6.9) Chills 6.1 (5.4-6.9) Body aches 8.6 (7.6-9.7) Dizzy 5.3 (4.6-6.3) Confusion 2.4 (1.6-3.5)		N=273 patients Community - Virtual Outpatient Management Clinic Mild, moderate & severe provider-assessed symptom severity USA Adults

Pre-print	Headache 8.2 (7.3-9.3) Smell/taste loss 11.0 (10.0-12.2) Congestion 9.0 (7.9-10.2) Sore throat 7.0 (6.0-8.2) Cough 12.2 (11.0-14) Chest tightness 8.0 (6.8-9.4) SOB with exert 8.8 (7.5-10.3) SOB a rest 5.0 (4.0-6.1) Wheezing 5.5 (4.3-7.1) Abd pain 4.5 (3.6-5.6) Nausea 6.0 (5.0-6.8) Diarrhea 5.8 (5.0-6.8) Joint pain7.7 (6.4-9.3) Rash 5.8 (4.8-5.3)		Mean age = 45.7 years
Omar[47] Retrospective cohort Standardized data collection by public health authorities		Median = 20 (IQR 16-28)	N=537 Community Severity not specified Germany Adults (mean age not provided)
Pongpirul[28] Prospective cohort Standardized data collection by HCW	Median=6 (IQR 4-11.5) Fever only Mean=7.0 (SD 3.9) Fever only Median=12 (IQR 9-13.5) All symptoms Mean=11.9 (SD 2.8) All symptoms	Median=14 (IQR 9-26) Mean = 16.5 (SD 9.1)	N=11 Hospital patients Severity not reported Thailand Adults Median age = 61 (range 28-74) Symptoms: cough, malaise, sore throat, rhinorrhea, headache, vomiting, diarrhea
Pullen[29] Prospective cohort Patient self-report (online)	Median = 5 (IQR 3-11)		N=316 Community patients Severity not specified USA Adults Median age = 45 (IQR 35-55) Symptoms: fever, dyspnea, headache, diarrhea, rhinorrhea, sore throat, fatigue, myalgia, sinus congestion, anosmia
Qi[48] Retrospective cohort Chart review		Median = 17 (IQR 12-21) (Range= 6-47)	N=147 Hospital patients Moderate & severe China Adults Median age = 42 (IQR 35-54) Symptoms: fever, cough, expectoration, hemoptysis
Romao[30] Prospective cohort Patient self-report	Mean Fever 7 (SD 9) Cough 25 (SD 14) Dyspnea 14 (SD 10)	Mean = 31 ± 10 (range: 15-51)	N=14 Healthcare workers Mild & moderate severity Portugal Mean age = 40 (±14)

	Chest tightness 22 (SD 16) Malaise 16 (SD 15) Fatigue 24 (SD 21) Headache 17 (SD 19) Rhinorrhea 24 (SD 17) Sore throat 9 (SD 9) Anosmia 16 (SD 13) Dysgeusia 12 (SD 7) Arthralgia 25 (SD 0) Myalgia 16 (SD 20) Nausea/V/D 13 (SD 12) Dizziness 10 (SD 8)		(range = 26-62)
Talmy[49] Prospective cohort Telephone data collection by HCW Pre-print		Median = 21 (IQR 15-27) (range 4-45) All symptoms Cough 21 (14-27) Smell loss 21 (15-27.5) Headache 21 (16-25.75) Taste Loss 23 (15-28) Fever 19 (15-25.5) Weakness 20 (15-30) Sore throat 20.5 (13-24.75) Rhinitis 20.5 (12.75-29.25) Myalgia 24 (17-33) Dyspnea 15 (12-24) Diarrhea 24 (17.75-29.25) Appetite Loss 23.5 (19.25-29.5) Nausea 26 (16-33) Chills 14 (12.25-23) Abd. pain 25 (21-32) Chest pain 21 (15-24) Rash 27 (18.5-35.5)	N=119 COVID rehabilitation centre patients Mild Israel Adults Median age = 21 (IQR 19-25)
van Kampen[50] Retrospective cohort Chart review Pre-print		Median = 8 (IQR 5-11) (range 0-20)	N=129 Hospital patients Severity not specified Netherlands Adults Median age=65 (IQR 57-72)
Woodruff [51] Retrospective cohort Chart review		Median = 28 (range 7-135) Mean = 31.6 (SD 16.7)	N=110 Community and hospital patients USA Adults Median age = 52 (range 17-86)
Xiao[52] Prospective cohort		Median = 24 (IQR 18-31)	N=56 Hospital patients Mild/moderate severity China Adults Median age = 55 (IQR42-68) (range 25-83)
Xu C.[53]		Mean = 11.1	N= 17 studies with 69 patients

Systematic review		(SD 5.8)	Hospital patients Mild & moderate severity Children Mean age = 6 years (range 36 hrs – 15 years)
Xu K.[54] Retrospective cohort Chart review		Median=17 (IQR 13-22)	N=113 Hospital patients Mild, moderate, severe China Adults Median age=52 (IQR 43-63)
Young[31] Retrospective cohort Chart review	Median All symptoms = 13 (range 5-24) Fever only = 4 (range 0-15)	Median = 12 (range 1-24)	N=18 Hospital patients Mild, moderate, severe China Adults Median age=47 (range 31-73) Symptoms: fever, cough, shortness of breath, rhinorrhea, sore throat, diarrhea
Zhou B.[55] Prospective cohort		Median=31 (IQR 24-40) (range 18-48)	N=41 Hospital patients Severe China Adults Median age=58 (IQR48-62)
Zhou F.[32] Retrospective cohort Chart review	Median Dyspnea=13 (IQR 9-16.5) Fever=12 (IQR 8-13) Cough=19 (IQR 12-23)	Median = 20 (IQR 17-24 (Range 8-37)	N=128 Hospital patients Mild, moderate, severe China Adults Median age=52 (IQR45-58) Symptoms: fever, cough, sputum, myalgia, fatigue, diarrhea, nausea, vomiting

Appendix

List of Abbreviations

Abd	Abdominal
Adj PLR	Adjusted Positive Likelihood Ratio
AHS	Alberta Health Services
AUC	Area Under the Curve
CI	Confidence Interval
COVID	SARS-CoV-2
Ct	Cycle Threshold Value
ED	Emergency Department
GI	Gastrointestinal
HCW	Healthcare Worker
ICU	Intensive Care Unit
ILI	Influenza-Like Illness
IQR	Interquartile Range
KRS	Knowledge Resource Services
LR	Likelihood Ratio
LRTI	Lower Respiratory Tract Infection
NPV	Negative Predictive Value
N/V/D	Nausea/Vomiting/Diarrhea
PCR	Polymerase Chain Reaction
PPV	Positive Predictive Value
OR	Odds Ratio
Resp	Respiratory
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SD	Standard Deviation
Sen	Sensitivity
SOB	Shortness of Breath
Spec	Specificity
URTI	Upper Respiratory Tract Infection
USA	United States of America

Methods

Literature Search

A literature search was conducted by Lauren Seal from Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services (AHS). KRS searched databases for articles published from January 1, 2020 to November 10, 2020, and included Medline, CINAHL, PubMed, TRIP Pro/Google Scholar/Google/CEBM/LitCovid/WHO Database/CDC/CADTH, and medRxiv. Manual searches from the reference lists of retrieved articles were also conducted. Relevant publications known to and suggested by AHS stakeholders were also included.

To determine symptoms which were predictive of a positive COVID-19 test result, included papers were limited to those which reported results from multivariate analyses, rather than descriptive or univariate analyses.

Included papers used for the summary of symptom and detectability duration were limited to those which explicitly stated “onset of symptoms” as the starting point for timeframe reporting. The timeframe endpoint was defined as the date of first of two consecutive negative RT-PCR test results. Papers were further limited to those that reported on RT-PCR test results were the samples were derived from respiratory system sources (oropharyngeal swabs, nasopharyngeal swabs, sputum samples or bronchoalveolar lavage samples).

Search Strategy

Question 1:

Medline

1 exp Coronavirus/ or Coronavirus Infections/ or coronaviru*.mp. or corona viru*.mp. or ncov*.mp. or n-cov*.mp. or novel cov*.mp. or COVID-19.mp. or COVID19.mp. or COVID-2019.mp. or COVID2019.mp. or SARS-CoV-2.mp. or SARSCoV-2.mp. or SARSCoV2.mp. or SARSCoV19.mp. or SARS-Cov-19.mp. or SARSCov-19.mp. or SARSCoV2019.mp. or SARS-Cov-2019.mp. or SARSCov-2019.mp. or severe acute respiratory syndrome coronaviru*.mp. or severe acute respiratory syndrome cov 2.mp. or 2019 ncov.mp. or 2019ncov.mp. or "severe acute respiratory syndrome*".mp. or "severe acute respiratory disease*".mp. or Severe Acute Respiratory Syndrome/ (70124)

2 exp "signs and symptoms"/ (2088048)
3 symptom?.mp. (1011204)
4 "clinical manifest*".mp. (68061)
5 "clinical feature*".mp. (106852)
6 2 or 3 or 4 or 5 (3028893)
7 positiv*.mp. (1888203)
8 exp Forecasting/ (86071)
9 "Predictive Value of Tests"/ (205596)
10 "predictive value*".mp. (279511)
11 predict*.mp. (1674093)
12 pre-test*.mp. (9998)
13 pretest*.mp. (17402)
14 presumptive.mp. (18194)
15 presumed.mp. (51939)
16 probable.mp. (78906)
17 probability.mp. (226473)
18 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (2068972)
19 1 and 6 and 7 and 18 (296)
20 limit 19 to yr="2020" (238)

CINAHL

S1 ((MH "Coronavirus+") OR (MH "Coronavirus Infections+") OR coronaviru* OR "corona virus" OR ncov* OR n-cov* OR ("2019 ncov" OR 2019ncov OR Hcov*)) OR (COVID-19 OR COVID19 OR COVID-2019 OR COVID2019) OR (SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019) OR (MH "Severe Acute Respiratory Syndrome") OR (("severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus*") OR "severe acute respiratory syndrome" OR "severe acute respiratory disease*") 29,675
S2 (MH "Signs and Symptoms+") 678,048
S3 symptom$ OR "clinical manifest*" OR "clinical feature*" 370,059
S4 positiv* 369,344
S5 (MH "Forecasting") OR (MH "Predictive Research") 17,834
S6 (MH "Predictive Value of Tests") 51,640
S7 "predictive value*" OR predict* OR pre-test* OR pretest* OR presumptive OR presumed OR probable OR probability 502,299
S8 S2 OR S3 961,847
S9 S5 OR S6 OR S7 512,454
S10 S1 AND S4 AND S8 AND S9 88
S11 S1 AND S4 AND S8 AND S9 Limiters - Published Date: 20200101-20201231 76

PubMed

("coronavirus"[MeSH Terms] OR "coronavirus infections"[MeSH Terms] OR "coronaviru*"[Title/Abstract] OR "corona virus*"[Title/Abstract] OR "ncov*"[Title/Abstract] OR "n cov*"[Title/Abstract] OR "novel cov*"[Title/Abstract] OR "covid-19"[Title/Abstract] OR "Covid19"[Title/Abstract] OR "covid-2019"[Title/Abstract] OR "covid2019"[Title/Abstract] OR "sars-cov-2"[Title/Abstract] OR "sarscov-2"[Title/Abstract] OR "sarscov2"[Title/Abstract] OR "sars-cov-2019"[Title/Abstract] OR "sarscov2019"[Title/Abstract] OR "sars-cov-19"[Title/Abstract] OR "sarscov19"[Title/Abstract] OR "severe acute respiratory syndrome coronaviru*"[Title/Abstract] OR "severe acute respiratory syndrome*"[Title/Abstract] OR "severe acute respiratory disease*"[Title/Abstract] OR "2019 ncov"[Title/Abstract] OR "2019ncov"[Title/Abstract] OR "severe acute respiratory syndrome"[MeSH Terms]) AND ("signs and symptoms"[MeSH Terms] OR "symptom"[Title/Abstract] OR "clinical feature*"[Title/Abstract] OR "clinical manifest*"[Title/Abstract]) AND "positiv*"[Title/Abstract] AND ("forecasting"[MeSH Terms] OR "predictive value of tests"[MeSH Terms] OR "predictive value*"[Title/Abstract] OR "predict*"[Title/Abstract] OR "pre test*"[Title/Abstract] OR "pretest*"[Title/Abstract] OR "presumptive"[Title/Abstract] OR "presumed"[Title/Abstract] OR "probable"[Title/Abstract] OR "probability"[Title/Abstract])

TRIP Pro/Google Scholar/Google/CEBM/LitCovid/WHO Database/CDC/CADTH

("covid-19" OR coronavirus OR “corona virus” OR sars-cov-2) AND (symptom OR symptoms OR “clinical features” OR “clinical manifestations”) AND (positive OR positivity) AND (predict OR predictive OR “predictive value” OR pre-test OR pretest OR presumed OR presumptive OR probable OR probability) from:2020

medRxiv

"(COVID-19 OR sars-cov-2 OR coronavirus) AND (positive) AND (predict OR probable OR pretest OR presumed)" and abstract or title "(symptom OR symptoms)" (match all words) and posted between "01 Jan, 2020 and 05 Nov, 2020"

Question 2:

Medline
1 exp Coronavirus/ or Coronavirus Infections/ or coronaviru*.mp. or corona viru*.mp. or ncov*.mp. or n-cov*.mp. or novel cov*.mp. or COVID-19.mp. or COVID19.mp. or COVID-2019.mp. or COVID2019.mp. or SARS-CoV-2.mp. or SARSCoV-2.mp. or SARSCoV2.mp. or SARSCoV19.mp. or SARS-Cov-19.mp. or SARSCov-19.mp. or SARSCoV2019.mp. or SARS-Cov-2019.mp. or SARSCov-2019.mp. or severe acute respiratory syndrome coronaviru*.mp. or severe acute respiratory syndrome cov 2.mp. or 2019 ncov.mp. or 2019ncov.mp. or "severe acute respiratory syndrome*".mp. or "severe acute respiratory disease*".mp. or Severe Acute Respiratory Syndrome/ (69865)
2 exp "signs and symptoms"/ (2088570)
3 symptom?.mp. (1011320)
4 "clinical manifest*".mp. (68066)
5 "clinical feature*".mp. (106872)
6 2 or 3 or 4 or 5 (3029473)
7 Time Factors/ (1194182)
8 (time adj2 course).mp. (76718)
9 (length adj2 time).mp. (15714)
10 (isolat* adj4 day*).mp. (6767)
11 (quarantine* adj4 day*).mp. (174)
12 (time adj2 infectious*).mp. (177)
13 (length adj2 infectious*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word,

protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (462)
14 (infect* adj3 period*).mp. (8894)
15 (symptom adj2 duration*).mp. (3542)
16 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (1284222)
17 1 and 6 and 16 (496)
18 limit 17 to yr="2020" (370)
19 from 18 keep 5,12,28,37,147,151,194,248,256,285,287,316,319,321,326,333,340,353 (18)

CINAHL
S1 ((MH "Coronavirus+") OR (MH "Coronavirus Infections+") OR coronaviru* OR "corona virus" OR ncov* OR n-cov* OR ("2019 ncov" OR 2019ncov OR Hcov*)) OR (COVID-19 OR COVID19 OR COVID-2019 OR COVID2019) OR (SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019) OR (MH "Severe Acute Respiratory Syndrome") OR (("severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus*") OR "severe acute respiratory syndrome" OR "severe acute respiratory disease*") 29,758
S2 (MH "Signs and Symptoms+") 678,069
S3 symptom$ OR "clinical manifest*" OR "clinical feature*" 370,091
S4 S2 OR S3 961,898
S5 (MH "Time Factors") 173,537
S6 time N2 course OR length N2 time OR isolat* N4 day* OR quarantine N4 day* OR time N2 infectious* OR length N2 infectious* OR infect* N3 period* OR symptom* N3 duration* 19,365
S7 S5 OR S6 189,928
S8 S1 AND S4 AND S7 168
S9 S1 AND S4 AND S7 Limiters - Published Date: 20200101-20201231 137

PubMed
("coronavirus"[MeSH Terms] OR "coronavirus infections"[MeSH Terms] OR "coronaviru*"[Title/Abstract] OR "corona virus*"[Title/Abstract] OR "ncov*"[Title/Abstract] OR "n cov*"[Title/Abstract] OR "novel cov*"[Title/Abstract] OR "covid-19"[Title/Abstract] OR "Covid19"[Title/Abstract] OR "covid-2019"[Title/Abstract] OR "covid2019"[Title/Abstract] OR "sars-cov-2"[Title/Abstract] OR "sarscov-2"[Title/Abstract] OR "sarscov2"[Title/Abstract] OR "sars-cov-2019"[Title/Abstract] OR "sarscov2019"[Title/Abstract] OR "sars-cov-19"[Title/Abstract] OR "sarscov19"[Title/Abstract] OR "severe acute respiratory syndrome coronaviru*"[Title/Abstract] OR "severe acute respiratory syndrome*"[Title/Abstract] OR "severe acute respiratory disease*"[Title/Abstract] OR "2019 ncov"[Title/Abstract] OR "2019ncov"[Title/Abstract] OR "severe acute respiratory syndrome"[MeSH Terms]) AND ("signs and symptoms"[MeSH Terms] OR "symptom"[Title/Abstract] OR "clinical feature*"[Title/Abstract] OR "clinical manifest*"[Title/Abstract]) AND ("time factors"[MeSH Terms] OR "time course"[Title/Abstract] OR "length of time"[Title/Abstract] OR "time length"[Title/Abstract] OR "isolation days"[Title/Abstract] OR "quarantine days"[Title/Abstract] OR "length infectious"[Title/Abstract] OR "infectivity period"[Title/Abstract] OR "symptom duration"[Title/Abstract] OR "duration of symptoms"[Title/Abstract])

TRIP Pro/Google Scholar/Google/CEBM/LitCovid/WHO Database/CDC/CADTH
("covid-19" OR coronavirus OR “corona virus” OR sars-cov-2) AND (symptom OR symptoms OR “clinical features” OR “clinical manifestations”) AND ("time factors" OR “time course” OR “quarantine length” OR "isolation days" OR "quarantine days" OR "infectivity period" OR “symptom duration” OR “duration of symptoms” OR “length infectious” OR duration OR time) from:2020

CEBM/LitCovid/WHO Database/CDC/CADTH
("time factors" OR “time course” OR “quarantine length” OR "isolation days" OR "quarantine days" OR "infectivity period" OR “symptom duration” OR “duration of symptoms” OR “length infectious” OR duration OR time)

Google Scholar/Google

("covid-19" OR coronavirus OR “corona virus” OR sars-cov-2) AND (symptom OR symptoms OR “clinical features” OR “clinical manifestations”) AND ("time factors" OR “time course” OR "isolation days" OR "quarantine day" OR duration)
("covid-19" OR coronavirus OR “corona virus” OR sars-cov-2) AND (symptom OR symptoms OR “clinical features” OR “clinical manifestations”) AND (time OR "isolation days" OR "quarantine day" OR duration)

medRxiv
"("time factors" OR “time course” OR "infectivity period" OR “symptom duration" OR duration)" and full text or abstract or title "("covid-19" OR coronavirus OR sars-cov-2) AND (symptom OR symptoms OR “clinical features” OR “clinical manifestations")" (match whole all) and posted between "01 Jan, 2020 and 09 Nov, 2020"

Question 3:

Medline/PubMed
1 exp Coronavirus/ or Coronavirus Infections/ or coronaviru*.mp. or corona viru*.mp. or ncov*.mp. or n-cov*.mp. or novel cov*.mp. or COVID-19.mp. or COVID19.mp. or COVID-2019.mp. or COVID2019.mp. or SARS-CoV-2.mp. or SARSCoV-2.mp. or SARSCoV2.mp. or SARSCoV19.mp. or SARS-Cov-19.mp. or SARSCov-19.mp. or SARSCoV2019.mp. or SARS-Cov-2019.mp. or SARSCov-2019.mp. or severe acute respiratory syndrome coronaviru*.mp. or severe acute respiratory syndrome cov 2.mp. or 2019 ncov.mp. or 2019ncov.mp. or "severe acute respiratory syndrome*".mp. or "severe acute respiratory disease*".mp. or Severe Acute Respiratory Syndrome/ (70528)
2 exp "signs and symptoms"/ (2088772)
3 symptom?.mp. (1011645)
4 "clinical manifest*".mp. (68091)
5 "clinical feature*".mp. (106908)
6 2 or 3 or 4 or 5 (3030023)
7 Time Factors/ (1194259)
8 (time adj2 course).mp. (76721)
9 (length adj2 time).mp. (15718)
10 (isolat* adj4 day*).mp. (6768)
11 (quarantine* adj4 day*).mp. (174)
12 (time adj2 infectious*).mp. (177)
13 (length adj2 infectious*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (462)
14 (infect* adj3 period*).mp. (8897)
15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (1281311)
16 exp "Sensitivity and Specificity"/ (591532)
17 exp Diagnostic Errors/ (117306)
18 "false negative*".mp. (44530)
19 "false positive*".mp. (74287)
20 "true negative".mp. (2632)
21 "true positive*".mp. (8152)
22 "positive predictive value*".mp. (46759)
23 "negative predictive value*".mp. (46508)
24 "test valid*".mp. (994)
25 detect*.mp. (2380431)
26 exp Polymerase Chain Reaction/ (450278)
27 PCR.mp. (516634)
28 RT-PCR.mp. (138271)
29 RTPCR.mp. (807)
30 "reverse transcript* polymerase chain*".mp. (196549)
31 duration.mp. (587021)

32 15 or 31 (1779121)
33 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (3379906)
34 1 and 6 and 32 and 33 (355)
35 limit 34 to yr="2020" (256)

CINAHL
S1 ((MH "Coronavirus+") OR (MH "Coronavirus Infections+") OR coronaviru* OR "corona virus" OR ncov* OR n-cov* OR ("2019 ncov" OR 2019ncov OR Hcov*)) OR (COVID-19 OR COVID19 OR COVID-2019 OR COVID2019) OR (SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019) OR (MH "Severe Acute Respiratory Syndrome") OR (("severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus*") OR "severe acute respiratory syndrome" OR "severe acute respiratory disease*") 30,242
S2 ((MH "Signs and Symptoms+")) OR (symptom$ OR "clinical manifest*" OR "clinical feature*") 962,564
S3 (MH "Time Factors") OR (time N2 course OR length N2 time OR isolat* N4 day* OR quarantine N4 day* OR time N2 infectious* OR length N2 infectious* OR infect* N3 period* OR symptom* N3 duration* OR duration) 306,513
S4 (MH "Sensitivity and Specificity") 84,652
S5 (MH "Diagnostic Errors+") 20,466
S6 (MH "Polymerase Chain Reaction+") 46,627
S7 "false negative*" OR "false positive*" OR "true negative*" OR "true positive*" OR "predictive value*" OR "test valid*" OR PCR OR RT-PCR OR RTPCR OR "reverse transcript* polymerase chain*" OR detect* 337,301
S8 S4 OR S5 OR S6 OR S7 414,721
S9 S1 AND S2 AND S3 AND S8 94
S10 S1 AND S2 AND S3 AND S8 Limiters - Published Date: 20200101-20201231 76

TRIP Pro/Google Scholar/Google/
("covid-19" OR coronavirus OR “corona virus” OR sars-cov-2) AND (symptom OR symptoms OR “clinical features” OR “clinical manifestations”) AND (time OR “quarantine length” OR "isolation days" OR "quarantine days" OR "infectivity period" OR duration “length infectious”) AND (“polymerase chain reaction” OR RT-PCR OR PCR OR RTPCR OR detectable OR detection OR detectability OR test) from:2020

Google Scholar
("covid-19" OR coronavirus OR “corona virus” OR sars-cov-2) AND (symptom OR symptoms) AND (time OR period OR length OR days OR duration) AND (“polymerase chain reaction” OR RT-PCR OR PCR OR RTPCR)
("covid-19" OR coronavirus OR “corona virus” OR sars-cov-2) AND (symptom OR symptoms) AND (time OR period OR length OR days OR duration) AND (detectable OR detect OR detection OR detectability OR test)

Google Advanced Search
("covid-19" OR coronavirus OR “corona virus” OR sars-cov-2) AND (symptom OR symptoms) AND (time OR period OR length OR days OR duration) AND (“polymerase chain reaction” OR RT-PCR OR PCR OR RTPCR OR detect OR detectable OR detectability OR test)

LitCovid/WHO Database/CEBM/LitCovid/WHO Database/CDC/CADTH
(symptom OR symptoms OR “clinical features” OR “clinical manifestations”) AND (time OR “quarantine length” OR "isolation days" OR "quarantine days" OR "infectivity period" OR duration “length infectious”) AND (“polymerase chain reaction” OR RT-PCR OR PCR OR RTPCR OR detectable OR detection OR detectability OR test
(symptom OR symptoms) AND (time OR duration OR length OR days) AND (detectability OR detectable OR detection) AND (test OR RT-PCR OR PCR OR RTPCR OR "polymerase chain reaction")

medRxiv
(time OR period OR duration) AND (detect OR detectable OR detection OR test OR "polymerase chain reaction" OR PCR)" and full text or abstract or title "(COVID-19 OR sars-cov-2 OR coronavirus) AND "(symptom OR symptoms)" (match whole all) and posted between "01 Jan, 2020 and 10 Nov, 2020"

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