Is the 14-day COVID-19 symptom-based test an accurate screening test to clear persons to return to work?

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Date of Review: June 11, 2020

This review summarizes the available evidence on the diagnostic performance of the 14-day symptom test in clearing persons for return to work. This may change as new evidence emerges.

KEY FINDINGS

Among asymptomatic individuals with possible exposure to COVID-19, the sensitivity of detecting active COVID19 infection with 14-day symptom-based test is 92.8% and specificity is 98.3%. The 14-day symptom-based test can be used for clearing workers to return to work.

- Many laboratory tests have been considered to screen for asymptomatic infectious individuals, including rapid antibody tests and RT-PCR. However, testing can also mean taking a clinical history or doing a physical examination. This rapid review evaluates a symptom-based test.
- The estimate of sensitivity was derived from direct evidence. We found 3 cohorts on the 14-day incidence of ILI among asymptomatic patients who tested positive for SARS-CoV-2 by RT-PCR.
- The estimate of specificity was derived from indirect evidence. We found 16 cohorts on the 14-day incidence of no ILI among asymptomatic patients during the pre-pandemic era. These cohorts came from the control group of 16 clinical trials on the influenza vaccine.
- These data support guidelines by DOH and several medical societies in the Philippines (PSMID, PCP, PSGIM, PMA, PSPHP, PAFP, PCOM) that recommend using the 14-day symptom test for clearing people to return to work. The CDC recommends a 14 day quarantine for asymptomatic individuals with exposure to COVID-19. The government of the United Kingdom and Australia and WHO likewise recommend a 14-day quarantine period for exposed workers.

BACKGROUND

Quarantine restrictions place a huge strain on the livelihood of every Filipino family and the Philippine economy as a whole. However, loosening lockdown restrictions may potentially cause a rise of another wave of cases, especially when people return to the workplace [1]. The objective of screening therefore, is to identify individuals who are potentially infectious and might put co-workers at risk of spreading COVID-19. Screening will involve conducting tests in asymptomatic individuals.

Many laboratory tests have been considered to screen for asymptomatic infectious individuals, including rapid antibody tests and RT-PCR. However, testing can also mean taking clinical history or doing a physical examination. This rapid review evaluates a symptom-based test, which is currently recommended by the World Health Organization (WHO) [2] , the Center for Disease Control and Prevention (CDC) [3], and locally by the PMA, PCP, PSMID, PCOM, PAFP and PSPHP [4]. This test involves asking people 2 questions before returning to work:

1) if they have been exposed through contact with known COVID-19 cases, or travel from areas with community transmission in the past 14 days; or
2) if they have had any symptoms of Influenza-Like Illness (ILI) in the past 14 days (fever, headache, cough, colds, sore throat, muscle pain, malaise, fatigue and other flu-like symptoms).

A yes to either question is a positive test which means that the patient could be infected and should be quarantined. A no to both questions is a negative test, which means infection is unlikely, and the worker can be cleared to return to work [4]. The rationale behind the recommendation comes from studies on the incubation period before developing COVID-19 symptoms [5]. Determining a maximum incubation period allows us to observe workers for a certain duration after exposure, beyond which infection becomes unlikely. They can then be cleared for work without conducting any laboratory tests.

Unfortunately, the approach to determining the incubation period of COVID-19 is through retrospective investigation of symptomatic patients. In effect, estimates of sensitivity are based on pre-symptomatic patients and may have failed to include those who never had symptoms within 14 days. To assure inclusion of both pre-symptomatic and never symptomatic patients, a prospective follow-up of exposed individuals is required, in this case, for 14 days. These studies are also needed for estimates of specificity. This rapid review attempts to find such prospective cohorts to determine the sensitivity and specificity of the 14-day symptom-based test.

OBJECTIVES

The objective of this review is to determine the sensitivity and specificity of a 14-day symptom-based test in detecting active SARS-COV-2 infection.

Definition of terms:

1. **Sensitivity** (Sn) or the true positive rate is defined as the proportion of RT-PCR SARS-CoV-2 positive patients who develop ILI within 14 days of exposure.

2. **Specificity** (Sp) or the true negative rate is defined as the proportion of RT-PCR SARS-CoV-2 negative patients who do not experience ILI within 14 days of exposure.

3. Influenza-like illness is defined as acute onset fever, headache, cough, colds, sore throat, muscle pain, malaise, or fatigue [6].

METHODS

The general methodologic approach to these rapid reviews has been described previously and is summarized here in brief.

To determine the accuracy of a symptom-based strategy for COVID-19, a comprehensive search was done of peer and non-peer reviewed journals published on the internet. Peer reviewed journals in PUBMED and MEDLINE and non-peer reviewed journals from MedRxIv were searched on June 9, 2020. The searches were individually conducted by three investigators (IC, PI, MM) and were appraised by two investigators (PI, MM). Disagreements were resolved by consulting two other investigators (LD, AD).

Articles were selected based on the following inclusion criteria:

Population: Healthy adults

The test: development of ILI within 14 days of exposure

The disease to be diagnosed: contagious SARS-CoV-2 infection

Study designs: Cohort studies or systematic reviews of cohort studies

Estimation of the Diagnostic Performance of the 14-day Symptom-Based Test

Stata 15.1 was used to pool the estimates of studies on sensitivity and specificity.

RESULTS

Characteristics of Included Studies

We found three cohort studies (n=234) that investigated sensitivity, that is, the proportion of SARS-CoV-2 positive patients who developed symptoms within 14 days from the time of exposure [7–9]. One study was conducted during an outbreak in a skilled nursing facility in the United States [7]. Another study studied household members of COVID-19 patients in Wuhan, China [8]. The last study included close contacts and patients admitted at a hospital for underlying disorders or surgical procedures in South Korea [9]. The details of these studies may be seen in Appendix 1. The list of excluded studies are listed in Appendix 2. It is important to note that studies were excluded when a follow-up period of 14 days of the COVID-19 patients were not stated in the reports.

For the estimation of specificity, we found no cohort studies on the incidence of ILI among patients who tested negative for COVID-19. Such studies would have provided the false positive rate (FPR) from which specificity could be calculated as 1-FPR. We found indirect evidence from the Department of Health (DOH) national incidence of ILI in 2019 (before the pandemic) [10] and from the control groups of 16 clinical trials on flu vaccine for the prevention of ILI in healthy adults. The trials were reported in a meta-analysis, and were all conducted during the pre-pandemic era, thus assuring there were no cases of COVID-19 [11].

From these 2 sources, we chose to use data from the trials because of more comprehensive and closer follow-up compared to our national statistics which typically suffer from underreporting. Furthermore, these trials reported the occurrence of ILI during the peak of influenza season (approximately 3 months), assuring a higher FPR and therefore, a more conservative estimate of specificity. As further assurance, we used the control group in these trials, where ILI incidence was higher. We computed for the 14-day Incidence rate for each individual study and pooled the incidence estimates to determine the false positive rate of the 14-day symptom-based test. An expanded definition of ILI was used in these trials as defined above.

SENSITIVITY

Symptomatic Cases within 14 days

The range of symptomatic patients in the three studies ranged from 91.5% to 93.8% [7-9]. The pooled proportion (n=234) of symptomatic SARS-CoV-2 positive cases who developed symptoms within 14 days is 92.8 (95% CI 89.5, 96.1, I^2 0%). Figure 1 illustrates the pooled proportion of symptomatic cases within 14 days.

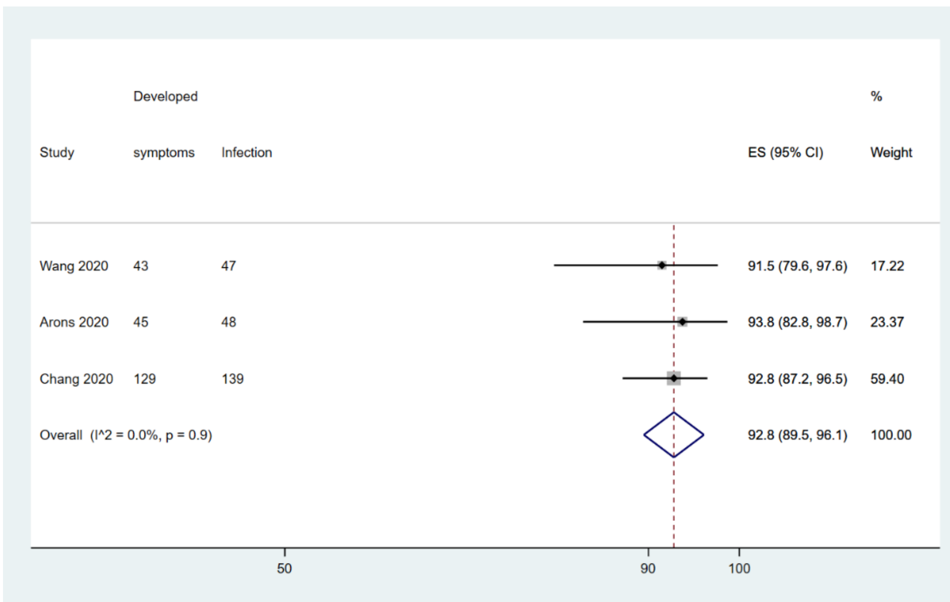

Figure 1. Pooled sensitivity of the 14-day symptom-based test

SPECIFICITY

Based on the review by Demichelli, 21.5% of unvaccinated participants developed symptoms of influenza-like-illness in their follow-up period [11]. From this data, we estimated the number of cases that would have ILI in 14 days for each individual study. The pooled 14-day incidence was 1.7% (95% CI 0.8, 2.8) (Figure 2). This is the presumed FPR, so specificity, calculated simply as 1-FPR is 98.3% (95% CI 97.2, 99.2) for the 14-day symptom-based test.

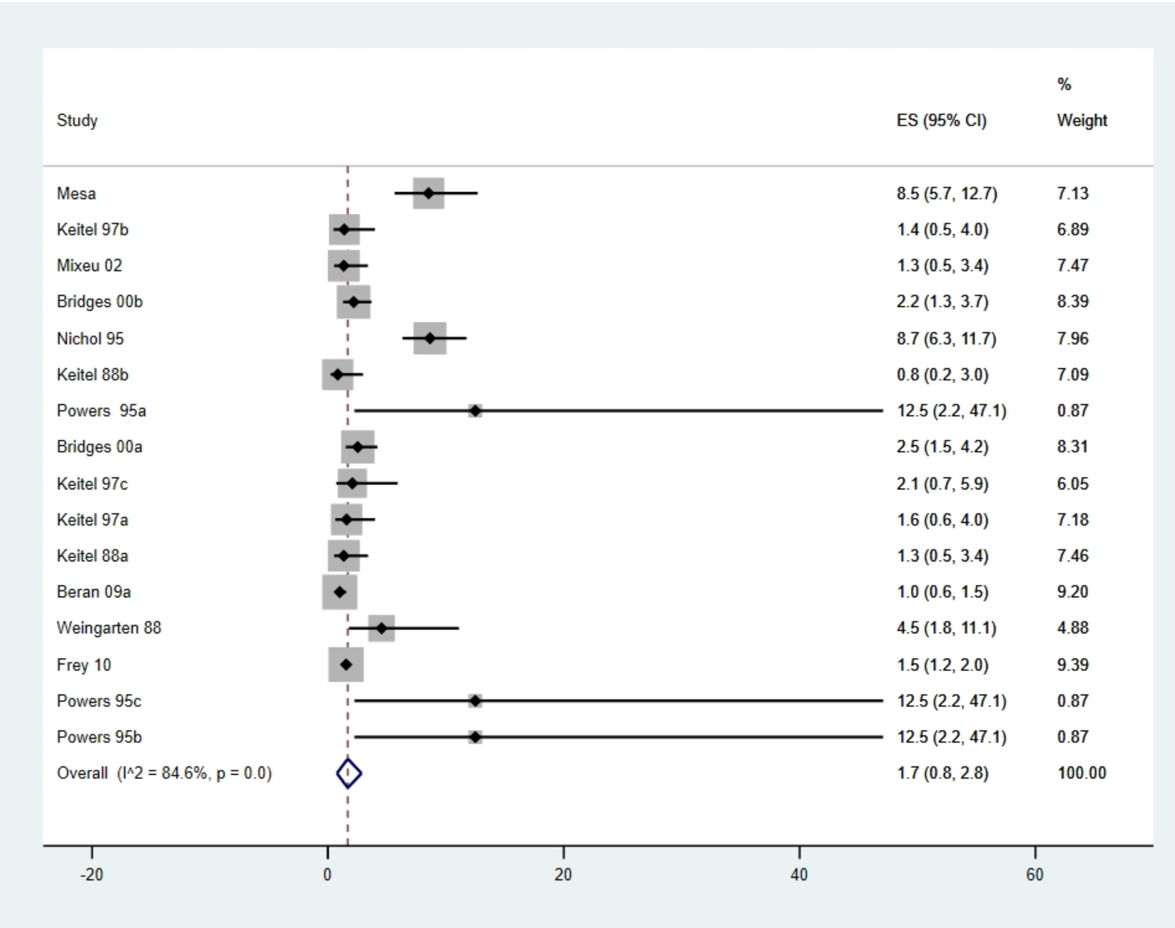

Figure 2. Pooled estimate of Incidence of Influenza-like Illnesses within 14 days

CRITICAL APPRAISAL OF STUDIES INVESTIGATED

The studies included in the estimation of the asymptomatic proportion of SARS-CoV-2 positive patients were of moderate quality. The follow-up period was adequate, however, one study was prone to sampling bias [8], because there were still asymptomatic persons who they failed to test. The populations studied were mostly patients who were in close contact with a known case of COVID-19. None of these studies were done for screening of the general population in areas with local transmission.

The meta-analysis used in computing specificity was of low quality [11]. The data are indirect and there was substantial heterogeneity in the pooled data (I2 = 84.6%, p = 0), attributable to the differences in the definition of influenza-like-illness and the differences in the timing when the studies were conducted in different geographic regions (Figure 2).

DISCUSSION

We found moderate quality data on sensitivity and poor quality data on specificity of the 14-day symptom-based test that screens for exposure and ILI. These data may be considered phase 2 validation data [12], in that the populations studied clearly have disease (for sensitivity) or no disease (for specificity). Patients in between, with diagnostic uncertainty, were not included. Because COVID-19 is a late-breaking phenomenon worldwide, this is not surprising. Most published evaluations of tests as of this date, are still phase 2 studies. For example, specificity of many laboratory tests are estimated using shelf blood obtained from the pre-pandemic period.

Symptoms are rarely evaluated prospectively like laboratory tests [13]. Often, only sensitivity of symptoms is known, from their prevalence in individuals who are known to have a certain condition [14]. The impact of these limitations is that we may be overestimating sensitivity and specificity of the 14-day symptom-based test. A phase 3 study may be in order to more accurately determine sensitivity and specificity in the real world. Such a study should recruit asymptomatic individuals including those undergoing safety clearance for return to work.

Nevertheless, the estimated sensitivity of 92.8% and specificity of 98.3% specificity are encouraging, and can justify current recommendations not to use laboratory tests to clear individuals for work.
The sensitivity of the 14-day symptom-based test for active infection is far better than reported pooled sensitivity of RATs which is 49.2% (95% CI: 41.1%, 57.4%) [16] (See Appendix 3a Screencapture). This means that RATs can miss as much half of asymptomatic infectious cases, compared to only 7.2% missed by the 14-day symptom-based test.

Pooled specificity of RATs for active infection (the first 2 weeks) is likewise poor at 27% (95% CI: 10.5%, 54.0%) [15] (See Appendix 3b Screencapture). This means that 73% of those who are truly COVID-19 negative will have a positive RAT result. While this may not seem as dangerous as false negatives (missed cases), the economic implications are enormous. First, this means that these workers will not be allowed to work for a while. Second, having had a positive RAT result, these workers will be required to undergo more expensive tests, presumably RT-PCR, which has its own limitations in asymptomatic patients [16]. Third, contact tracing will be performed by already undermanned government teams or company health teams. Fourth, many contacts of these workers may be wrongly quarantined. Fifth, there might be unnecessary anxiety of falsely being diagnosed with a stigmatized infection. Sixth and last, affected workers may get a false sense of immunity after their isolation period.

Applicability Issues of the 14-day Symptom-Based Strategy

There are issues on applicability of the 14-day symptom-based test that need to be pointed out. First, the 14-day screening test is most applicable in persons with known contact with a confirmed COVID-19 case (i.e. healthcare workers) and those who have been exposed to areas of high COVID-19 transmission. Therefore, the extent of local transmission in a particular community should be known, as well as the history of recent contacts.

Second, sensitivity can be diminished by **symptom denial**. Workers may not disclose their symptoms, in order to avoid discrimination or economic consequences. Several strategies can help minimize symptom denial [17] :

1. Workers and employees must be educated about COVID-19, its signs and symptoms, and mode of transmission;
2. Workers and employees must be assured that symptom admission protects everyone, including their family, their community and their co-workers;
3. Adequate sick leave payment must be provided for employees, and unemployment benefits for other workers;
4. Employers must provide work-from-home options when possible, for employees under quarantine or isolation;
5. Workers and employees must be assured of healthcare benefits should they present with influenza-like illness or COVID-19 symptoms; and

6. Companies must discourage employee presenteeism, or the practice of coming to work despite feeling ill.

These conditions must define the new normal in employer-employee and worker-client relationships. Without such trust, employers and workers will need to undergo laboratory tests not just on their initial return to work but every day until the pandemic ends.

Recommendations from Other Guidelines

Several guidelines give recommendations for employers of healthcare and non-healthcare facilities to decide if their workers are safe to return to work. Most recommend a symptom-based approach over a laboratory test-based measure.

Philippine Department of Health Guidelines (DOH)

As per DOH Circular 2020-0220 [18], Filipino workers are allowed to return to work if they have no exposure or symptoms in the past 14 days. Those who have been exposed or have symptoms should consult with their primary care provider for clearance. Testing is not considered necessary but employers may opt to test their workers with RT-PCR and antibody testing. However, the DOH recognizes the lack of reliability and validity of such methods.

Return to Work Statement from Different Medical Associations in the Philippines

The Philippine Society for Microbiology and Infectious Diseases (PSMID) posted in their official website on May 22, 2020, a unified statement along with the Philippine College of Physicians (PCP), Philippine Society of General Internal Medicine (PSGIM), Philippine Medical Association (PMA), Philippine Society of Public Health Physicians (PSPHP), Philippine Academy of Family Physicians (PAFP), and Philippine College of Occupational Medicine (PCOM) [4]. The societies released a joint statement recommending the **14-day symptom-based test** in clearing people to return to work. They do not recommend the use of rapid antibody tests (RATs) for screening due to their impracticality, low sensitivity and high false-positive rates.

The United States Centers for Disease Control and Prevention (US CDC)

The US Centers for Disease Control and Prevention (CDC) recommended [3] that healthy individuals with possible exposure should quarantine themselves, check their temperature twice a day and watch for symptoms of COVID-19 for 14 days. CDC cautioned that no decision policy will ensure that 100% of patients will no longer be infectious but based their decision on the best available data.

Other countries

The governments of Australia and the United Kingdom also recommend a mandatory 14-day quarantine period for exposed workers who wish to return to work [19, 20].

CONCLUSION

Based on phase 2 validation studies, the 14-day symptom-based test has a sensitivity of 92.8% and a specificity of 98.3%. A symptom-based strategy is a practical and accurate approach in clearing persons to return to work. A prospective phase III validation study using the 14-day symptom-based test is recommended. Meanwhile current recommendations on using the 14-day symptom-based test are consistent with existing information on the course of COVID-19. Workplaces must institute policies to ensure that employees feel safe in disclosing their symptoms.

Declaration of Conflict of Interest

No conflict of interest

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Appendix 1. Characteristics of included studies for the estimation of Sensitivity of 14-day Symptom-based Test

No.	Title	Study design	Country	Population	Reason for testing	Test(s) done	Proportion of Asymptomatic Cases beyond 14 days	Symptoms monitored
1	Chest Computed Tomography Findings in Asymptomatic Patients with COVID-19 Chang 2020	Retrospective study	South Korea	Hospitalized COVID-19 patients	• Contact history • Routine laboratory test on admission for treating other underlying disorders • Routine COVID 19 test before surgery	RT PCR (pharyngeal swab)	10 of 139 (7.19%, 95% CI 3.5, 12.83)	None mentioned
2	Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility Arons 2020	Prevalence study	Washington, USA	Skilled nursing facility residents	Close contact	NPS and OPS RT PCR, viral culture, sequencing	3 of 48 (11.11%, 95% CI 2.35, 29.16)	Fever, cough, and shortness of breath, chills, malaise, sore throat, increased confusion, rhinorrhea or nasal congestion, myalgia, dizziness, headache, nausea, and diarrhea.
3	Household transmission of SARS-CoV-2 Wang 2020	Retrospective cohort study	Wuhan, China	Household contacts of COVID-19 patients	Close contact	RT PCR throat swab	4 of 47 (8.51%, 95% CI 2.37, 20. 38)	Fever, cough, fatigue, myalgia, dyspnea, sputum production, diarrhea, and headache

Appendix 2. Excluded studies

Title	Country	Duration of follow-up or observation period	Reason for exclusion
Tong ZD, Tang A, Li KF, Li P, Wang HL, Yi JP, et al. Potential Presymptomatic Transmission of SARS-CoV-2, Zhejiang Province, China, 2020. Emerg Infect Dis [Internet]. 2020 [cited 2020 Jun 13]; 26(5). Available from: https://wwwnc.cdc.gov/eid/article/26/5/20-0198_article doi:10.3201/eid2605.200198	China	Until negative PCR result	Variable duration of observation period, low sample size (5)
Liao J, Fan S, Chen J, Wu J, Xu S, Guo Y, et al. Epidemiological and clinical characteristics of COVID-19 in adolescents and young adults. The Innovation [Internet]. 2020 [cited 2020 Jun 13]; 1(1). Available from: https://www.sciencedirect.com/science/article/pii/S2666675820300011 doi: 10.1101/2020.03.10.20032136	China	Until February 23	Unclear duration of follow-up for asymptomatic patients
Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020 [cited 13 Jun 2020]; 63(5):706-11. Available from: https://pubmed.ncbi.nlm.nih.gov/32146694/ doi: 10.1007/s11427-020-1661-4.	China	Until February 18 (not clear)	Unclear duration of follow-up for asymptomatic patients, low sample size (4)
Luo SH., Liu W, Liu ZJ, Zheng, XY, Hong CX, Liu, ZR et al. (2020). A confirmed asymptomatic carrier of 2019 novel coronavirus. Chin Med J [Internet]. 2020 [cited 2020 Jun 13]; 133(9):1123–1125. Available from: https://journals.lww.com/cmj/fulltext/2020/05050/a_confirmed_asymptomatic_carrier_of_2019_novel.21.aspx doi:10.1097/CM9.0000000000000798	China	Entire hospitalization	Unclear duration of observation period for asymptomatic cases, low sample size (5)
Chan JF, Yuan S, Kok KH, To KKW, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet [Internet]. 2020 [cited 2020 Jun 13];395(10223):514-23. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30154-9/fulltext doi: 10.1016/S0140-6736(20)30154-9	China	Not clear	Unclear duration of follow-up for asymptomatic patients, low sample size (5)
Ye F, Xu S, Rong Z, Xu R, Liu X, Deng P, et al. Delivery of infection from asymptomatic carriers of COVID-19 in a familial cluster. Int J Infect Dis [Internet]. 2020 [cited 2020 Jun 13];94:133-38. Available from: https://www.ijidonline.com/article/S1201-9712(20)30174-0/fulltext doi: 10.1016/j.ijid.2020.03.042	China	14 days since exposure	Low sample size (5)

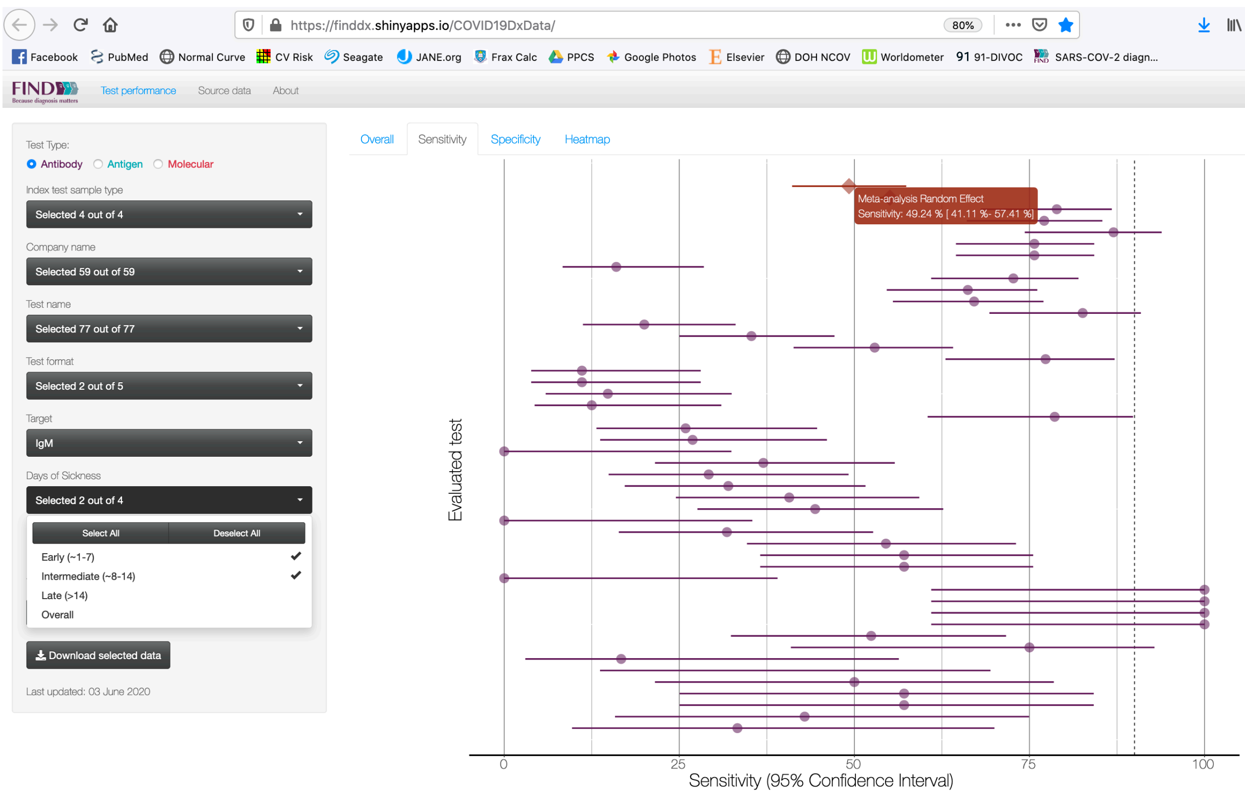
Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA [Internet]. 2020 [cited 2020 Jun 13];54(0):E017. Available from: https://jamanetwork.com/journals/jama/fullarticle/2762028 doi: 10.1001/jama.2020.2565	China	10-14 days after exposure (variable)	Patients were symptomatic when tested, only a presumptive exposure (index case initially tested negative)
Le TQM, Takemura T, Moi ML, Nabeshima T, Nguyen LKH, Hoang VMP, et al. Severe Acute Respiratory Syndrome Coronavirus 2 Shedding by Travelers, Vietnam, 2020. Emerg Infect Dis [Internet]. 2020 [cited 2020 Jun 13];26(7). Available from https://wwwnc.cdc.gov/eid/article/26/7/20-0591_article doi: 10.3201/eid2607.200591	Vietnam	>14 days after exposure	Small sample size (6)
Zhang J, Tian S, Lou J. Familial cluster of COVID-19 infection from an asymptomatic. Crit Care [Internet]. 2020 [cited 2020 Jun 13];24. Available from: https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-2817-7 doi: 10.1186/s13054-020-2817-7	China	~1 month after exposure	Small sample size (4)
Qian G, Yang N, Ma AHY, et al. A COVID-19 Transmission within a family cluster by presymptomatic infectors in China. Clin Infect Dis [Internet]. 2020 [cited 2020 Jun 13]. Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa316/5810900 doi: 10.1093/cid/ciaa316	China	Less than 14 days since last day of exposure	Short duration of follow-up, small sample size (7)
Luo L, Liu D, Liao X-l, et al. Modes of contact and risk of transmission in COVID-19 among close contacts. medRxiv [Internet]. 2020 [cited 13 Jun 2020]. Available from: https://www.medrxiv.org/content/10.1101/2020.03.24.20042606v1 doi: 10.1101/2020.03.24.20042606	China	Variable, followed-up until with negative swab	Variable duration of observation period
Yang N, Shen Y, Shi C, Ma AHY, Zhang X, Jian X, et al. In-flight transmission cluster of COVID-19: A retrospective case series. medRxiv [Internet]. 2020 [cited 2020 Jun 13]. Available from: https://www.medrxiv.org/content/10.1101/2020.03.28.20040097v1 doi: 10.1101/2020.03.28.20040097	China	14 days after exposure	Small sample size (10)
Kimball A, Hatfield KM, Arons M, et al. Asymptomatic and presymptomatic SARS-CoV-2 infections in residents of a long-term care skilled nursing facility - King County, Washington, March 2020. MMWR Morb Mortal Wkly Rep [Internet]. 2020 [cited 2020 Jun 13]; 69(13):377-81. Available from https://www.cdc.gov/mmwr/volumes/69/wr/mm6913e1.htm doi: 10.15585/mmwr.mm6913e1	USA	7 days after diagnosis	Short duration of observation period
Tian S, Wu M, Chang Z, Wang Y, Zhou G, Zhang W, et al. Epidemiological investigation and intergenerational clinical characteristics of 24 COVID-19 patients associated with supermarket cluster. medRxiv [Internet]. 2020 [cited 2020 Jun 13]. Available from: https://www.medrxiv.org/content/10.1101/2020.04.11.20058891v1 doi: 10.1101/2020.04.11.20058891	China	14 days after exposure and until negative PCR result	Variable duration of observation period
Hoehl S, Rabenau H, Berger A, Kortenbusch M, Cinatl J, Bojkova D, et al. Evidence of SARS-CoV-2 infection in returning travelers from Wuhan, China. N Engl J Med [Internet]. 2020 [cited 2020 Jun 13]; 382(13):1278-80. Available from: https://www.nejm.org/doi/full/10.1056/NEJMc2001899 doi: 10.1056/NEJMc2001899	Germany	7 days after diagnosis	Short follow-up period

Chang L, Zhao L, Gong H, Wang L, Wang L. Severe acute respiratory syndrome coronavirus 2 RNA detected in blood donations. Emerg Infect Dis [Internet]. 2020 [cited 2020 Jun 13]; 26(7). Available from https://wwwnc.cdc.gov/eid/article/26/7/20-0839_article doi: 10.3201/eid2607.200839	China	7 days after diagnosis	Unclear exposure date
Pongpirul WA, Mott JA, Woodring JV, Uyeki TM, MacArthur JR, Vachiraphan A, et al. Clinical characteristics of patients hospitalized with coronavirus disease, Thailand. Emerg Infect Dis [Internet]. 2020 [cited 2020 Jun 13]; 26(7). Available from: https://wwwnc.cdc.gov/eid/article/26/7/20-0598_article doi: 10.3201/eid2607.200598	Thailand	Until negative PCR result	Variable observation period
Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med [Internet]. 2020 [cited 2020 Jun 13]; 382(12):1177-79. Available from https://www.nejm.org/doi/full/10.1056/NEJMc2001737 doi: 10.1056/NEJMc2001737	China	None stated	Unclear follow-up period
Wang X, Fang J, Zhu Y, Chen L, Ding F, Zhou R, et al. Clinical characteristics of non-critically ill patients with novel coronavirus infection (COVID-19) in a Fangcang Hospital. Clin Microbiol Infect [Internet]. 2020 [cited 2020 Jun 13]. Available from: https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30177-4/fulltext doi:10.1016/j.cmi.2020.03.032	China	Until February 22	Unclear onset of exposure
Tabata S, Imai K, Kawano S Ikeda M, Kodama T, Miyoshi K, et al. Non-severe vs severe symptomatic COVID-19: 104 cases from the outbreak on the cruise ship 'Diamond Princess' in Japan. medRxiv [Internet]. 2020 [cited 2020 Jun 13]. Available from: https://www.medrxiv.org/content/10.1101/2020.03.18.20038125v2 doi: 10.1101/2020.03.18.20038125	Japan	1-15 days after admission	Variable observation period
See KC, Liew SM, Ng DCE, Chew EL, Khoo EM, Sam CH, et al. COVID-19: Four paediatric cases in Malaysia. Int J Infect Dis [Internet]. 2020 [cited 2020 Jun 13]; 94:125-27. Available from: https://www.sciencedirect.com/science/article/pii/S1201971220301818 doi: 10.1016/j.ijid.2020.03.049	Malaysia	Until negative PCR	Small sample size (4)
Tan YP, Tan BY, Pan J, Wu J, Zeng S, Wei H. Epidemiologic and clinical characteristics of 10 children with coronavirus disease 2019 in Changsha, China. J Clin Virol [Internet]. 2020 [cited 2020 Jun 13]; 127:104353. Available from: https://www.sciencedirect.com/science/article/pii/S1386653220300950?via%3Dihub doi: 10.1016/j.jcv.2020.104353	China	7 days after diagnosis and until negative PCR result	Variable observation period, small sample size (10)
Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis [Internet]. 2020 [cited 2020 Jun 13]. Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30198-5/fulltext doi: 10.1016/S1473-3099(20)30198-5	China	14 days after exposure, 7 days after diagnosis, until negative PCR	Unclear if they monitored symptom progression in asymptomatic individuals
Wang Y, Tong J, Qin Y, Xie T, Li J, Li J, Xiang J, Cui Y, Higgs ES, Xiang J, He Y, Characterization of an asymptomatic cohort of SARS-COV-2 infected individuals outside of Wuhan, China, Clin Infect Dis [Internet]. 2020 [cited 2020 Jun 13]. Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa629/5842166 doi: 10.1093/cid/ciaa629	China	Until discharge at hospital	Variable observation period
London V, McLaren R Jr, Atallah F, Cepeda C, McCalla S, Fisher N, et al. The relationship between status at presentation and outcomes among pregnant women with COVID-19. Am J Perinatol [Internet]. 2020 [cited	New York, USA	10 days follow-up after discharge	Short observation period

2020 Jun 13]. Available from: https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0040-1712164 doi:10.1055/s-0040-1712164			
Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Euro surveillance [Internet]. 2020 [cited 2020 Jun 13]; *25*(10). Available from https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.10.2000180 doi: 10.2807/1560-7917.ES.2020.25.10.2000180	Japan	No follow-up stated	No observation period
Kim GU, Kim MJ, Ra SH, Lee J, Bae S, Jung J, et al. Clinical characteristics of asymptomatic and symptomatic patients with mild COVID-19. Clin Microbiol Infect [Internet]. 2020 [cited 2020 Jun 13]. Available from: https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30268-8/fulltext doi:10.1016/j.cmi.2020.04.040	South Korea	No follow-up stated	No observation period
Nishiura H, Kobayashi T, Miyama T, Suzuki A, Jung SM, Hayashi K, et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). Int J Infect Dis [Internet]. 2020 [cited 2020 Jun 13]; 94:154–155. Available from: https://www.ijidonline.com/article/S1201-9712(20)30139-9/pdf doi: 10.1016/j.ijid.2020.03.020	Japan	No follow-up stated	No observation period
Lu X, Zhang L, Du H, Shen K, Zu S, Wong GWK, et al. SARS-CoV-2 infection in children. N Engl J Med [Internet]. 2020 [cited 2020 Jun 13]; 382(17):1663-1665.Available from: https://www.nejm.org/doi/full/10.1056/NEJMc2005073 doi:10.1056/NEJMc2005073	China	Until March 8	Unclear observation period
Ma Y, Xu QN, Wang FL, Ma XM, Wang XY, Zhang XG, Zhang, ZF. Characteristics of asymptomatic patients with SARS-CoV-2 infection in Jinan, China. Microb Infect [Internet]. 2020 [cited 2020 Jun 13]. S1286-4579(20)30078-2. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7204664/ doi: 10.1016/j.micinf.2020.04.011	China	Until March 10	Unclear observation period
He G, Sun W, Fang P, Huang J, Gamber M, Cai J, Wu J. The clinical feature of silent infections of novel coronavirus infection (COVID-19) in Wenzhou. J Med Virol [Internet]. 2020 [cited 2020 Jun 13]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25861 doi: 10.1002/jmv.25861	China	Until full recovery	Variable observation period
Olalla J, Correa AM, Martin-Escalante MD, Hortas ML, Martin Sendarrubias MJ, Fuentes V, Sena G, Garcia-Alegria J. Search for asymptomatic carriers of SARS-CoV-2 in healthcare workers during the pandemic: a Spanish experience. MedRxIV.[Internet]. 2020 [cited 2020 Jun 13]. Available from: https://www.medrxiv.org/content/10.1101/2020.05.18.20103283v1 doi: 10.1101/2020.05.18.20103283	Spain	No follow-up stated	Unclear observation period
Song H, Xiao J, Qiu J, Yin J, Yang H, Shi R, Zhang W. A considerable proportion of individuals with asymptomatic SARS-CoV-2 infection in Tibetan population. MedRxlv [internet]. 2020 [cited 2020 Jun 13]. Available from: https://www.medrxiv.org/content/10.1101/2020.03.27.20043836v1 doi: 10.1101/2020.03.27.20043836	China	Follow-up done until March 6, 2020	Unclear observation period
Daniel P. Oran, AM, and Eric J. Topol, MD. Prevalence of Asymptomatic SARS-CoV-2 Infection A Narrative Review Ann Intern Med. doi:10.7326/M20-3012	Italy	2 serial surveys with mean serial interval was 6.9 days	Short observation period

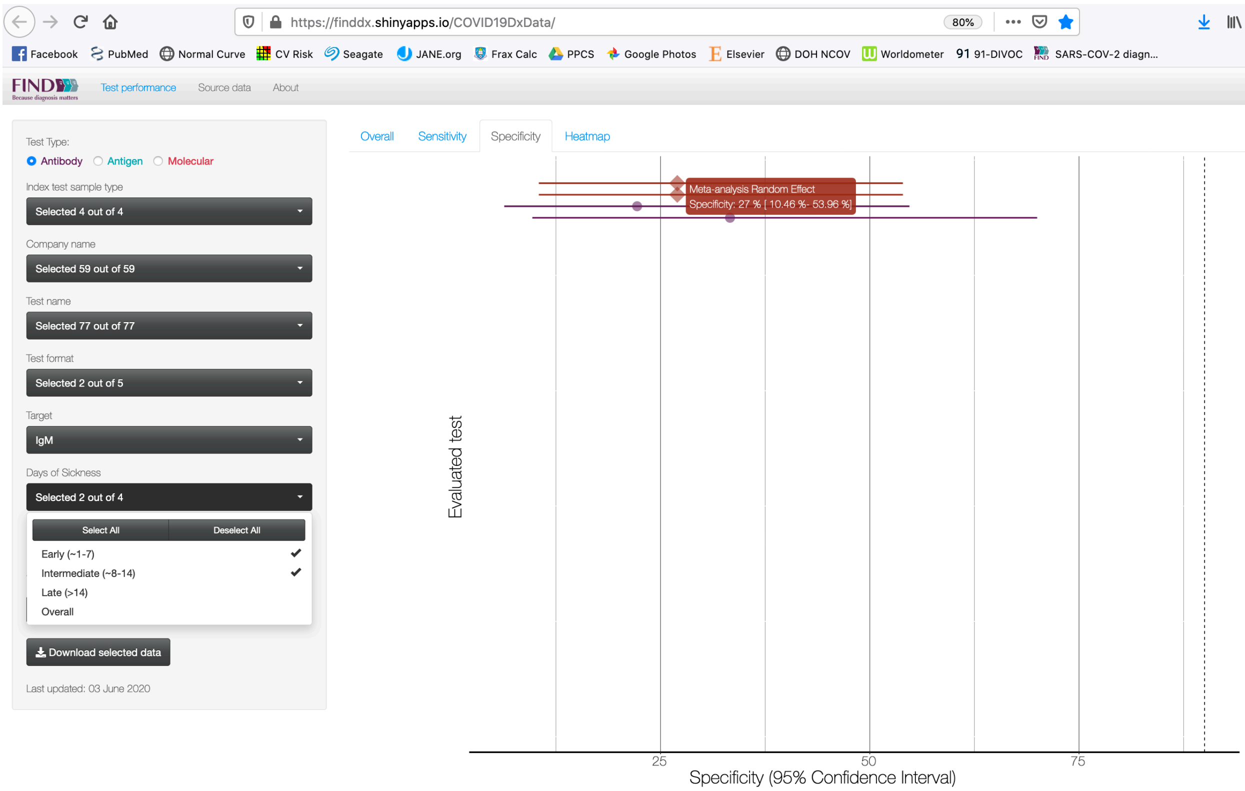
Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARSCoV-2 in the Icelandic population. N Engl J Med. 2020. [PMID:32289214] doi:10.1056/NEJMoa2006100	Iceland	open-invitation and random-population screening,.	Unclear observation period
Moriarty LF, Plucinski MM, Marston BJ, et al; CDC Cruise Ship Response Team. Public health responses to COVID-19 outbreaks on cruise ships — worldwide, February–March 2020. MMWR Morb Mortal Wkly Rep. 2020;69:347-352. [PMID: 32214086] doi:10.15585/mmwr.mm6912e3	Japan (Diamond Princess cruise ship)	16 March initial test but only statistical modelling for subsequent estimates	Unclear observation period
Sutton D, Fuchs K, D'Alton M, et al. Universal screening for SARSCoV- 2 in women admitted for delivery [Letter]. N Engl J Med. 2020; 382:2163-2164. [PMID: 32283004] doi:10.1056/NEJMc2009316	New York, USA	Median length of stay, 2 days).	Short observation period
Lytras T, Dellis G, Flountzi A, et al. High prevalence of SARSCoV-2 infection in repatriation flights to Greece from three European countries. J Travel Med. 2020;27. [PMID: 32297940] doi:10.1093/jtm/taaa054	Europe	Tested in airport or hotel	Unclear observation period

Appendix 3a Screencaptures from FIND (Foundation for Innovative New Diagnostics) https://finddx.shinyapps.io/COVID19DxData/ accessed 06/07/20.



Ref: Accessed 06/07/20

Appendix 3b Screencaptures from FIND (Foundation for Innovative New Diagnostics) https://finddx.shinyapps.io/COVID19DxData/ accessed 06/07/20.



Ref: Accessed 06/07/20