| Use Case | Description | Other Possible Technologies Required | Samples | Comments |
| --- | --- | --- | --- | --- |
| 1. Triage of symptomatic individuals in an epidemic setting
 | * The intended use is to determine if a symptomatic individual in an epidemic setting has a reasonable likelihood of a current SARS-CoV-2 virus infection warranting temporary isolation pending confirmatory testing
* Target use settings can be divided into two groups:
	+ Group 1: Sites with temporary (days) or fulltime residents such as assisted living centers, cruise ships, hospitals, prisons and quarantine facilities.
	+ Group 2: Settings could include public and community health centers, primary care facilities, urgent care clinics, and emergency departments in outbreak areas where symptomatic individuals could be expected to visit for work-up.
	+ Confirmation testing is required and is described in Use Case 4
 | * No triage tests for COVID-19 exist today
* Typically, a confirmatory test using different targets is needed, unless triage test clinical performance is very high
* It is possible that home self-tests will be deployed for triage — where positive results are not diagnostic, but will indicate that the individual should go to an appropriate confirmatory testing center or healthcare facility
* Information and communications technologies (ICT) to capture and report data for reporting to other stakeholders is needed (e.g. healthcare workers, MOH, Public Health, CDC, WHO).
* It is conceivable that a well-structured questionnaire or risk calculator could be used instead of or in addition to medical tests to deliver adequate performance (see Use Case 10)
 | * It may not be practical to obtain and process all sample types in all settings. “Sample-to-results” procedures should be carefully considered and matched to the end user capabilities.
* For self-tests or self-collection, saliva or nasal swabs (not nasopharyngeal) are preferred
* Simple low-cost biological targets such as blood cells or breath VOCs could be employed where finger prick blood or breath could be acceptable samples

  | * The turnaround time should be maximally 1 hour, preferably 15 minutes or less
* Decentralized testing is the preferred option for rapid turnaround, prevention of loss to follow-up and other reasons.
* The potential use of a triage test in an epidemic setting is tied to the availability of an acceptable confirmation test. Confirmatory testing solutions and algorithms appropriate for the intended use setting should be recommended.
* Confirmation testing will not always be available at the site of triage testing. In this situation, it could be necessary for the individual to be isolated near the site of testing or at home until send-out confirmation test results are obtained.
* The intended use settings can be roughly divided into two groups with different testing requirements.
	+ In Group 1 sites, individuals can likely be isolated and confirmation testing can be conducted remotely (multi-day send out);
	+ In Group 2 sites, remote confirmation testing is more problematic unless it can be conducted on site and rapidly. With send out testing it will not be possible to keep subjects on site long enough to isolate them to prevent potential transmissions.
* A triage test that permits the majority of symptomatic subjects to leave if they have a negative result (low probability of SARS CoV-2 infection; high sensitivity, high negative predictive value) would limit the need to isolate and test for confirmation of infection.
* On the other hand, the test requires an acceptable specificity so that few people are unnecessarily isolated and referred for confirmation testing. Even in an epidemic setting it is likely that most persons with symptoms do not have COVID-19. A high false positive rate, especially in populations with low prevalence, would waste a significant number of scarce, high-value RNA tests.
* In most of the intended use settings, a point of care (POC) format test is desirable, ideally one that is designed to meet CLIA-waiver requirements.
* While an instrument-free format has merit in many target use settings, the desire to capture and communicate information as well as features delivering improved test performance may favor automated solutions.
* Tests designed for decentralized POC testing should take into account the requirements across the wide variety of potential testing locations, environments, operators and regulatory requirements.
* It is likely that medical practitioners and technical staff in the target use settings will be wearing some form of personal protective equipment (PPE), which has implications for the type of sample that can be obtained (e.g., finger prick blood or nasal swabs while wearing gloves), how it can be processed (e.g., micro-capillary manipulation observation while wearing a mask) and the operator interfaces on the devices used (e.g., sample addition and touch screen while wearing gloves).
* Pressure to reduce pricing is increasing. Price targets\* (to the end user) are likely to be well under$25 USD for the US, but considerably less in low and middle-income countries (LMICs).
* Frequently in high income countries (HIC), established reimbursement is dependent on the type of assay technology used.
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| 1. Triage of symptomatic individuals in endemic settings
 | * The intended use is to determine if a symptomatic individual in an endemic setting has a reasonable likelihood of a current SARS-CoV-2 virus infection warranting temporary isolation pending confirmatory testing
* Intended use settings include both Groups 1 and 2 from Use Case 1, as well as all other sites where individuals could present seeking primary care
* Confirmation testing is required and described in Use Case 4
 | * Same as above
 | * Same as above
 | * This scenario assumes the SARS-CoV-2 virus will remain a recurring threat, requiring ongoing potential testing of individuals presenting with respiratory symptoms. Note: this comment is pertinent to all the remaining Use Cases
* Decentralized testing is a preferred option for rapid turnaround, prevention of loss to follow-up and other reasons.
* The disappearance and reappearance of SARS-CoV-2 from the local population could be due to a seasonal nature of the disease or effective elimination followed by reintroduction from infected individuals coming from other settings of current infections
* Most individuals presenting with symptoms under this scenario are less likely to be infected with SARS-CoV-2 than in the epidemic setting scenario. Common cold, flu, seasonal allergies or febrile diseases with similar clinical presentations will be more common, creating the potential need for diagnostic confirmatory testing and/or differential diagnostics.
* The turnaround time should be maximally 1 hour, preferably 15 minutes or less
* The need for high sensitivity remains, but in this scenario, there is also the need for higher specificity since in a low prevalence environment the majority of individuals could be false positives. A high percentage of false positives, especially relative to the prevalence in the region, would mean many more confirmatory and/or differential diagnostic tests are performed than are required.
* In these use settings, isolation will become a major annoyance and a likely impediment to testing. Therefore, is it important that confirmation testing be rapid, preferably offered at the site of triage testing.
* Due to performance limitations, it is possible that triage testing will not be ideal in some endemic settings where diagnostic tests (Use Case 5) would offer a more appropriate testing solution.
* For broadest utility, it is preferable that the test be CLIA-waivable for use by minimally trained users in decentralized testing settings.
* See additional comments in Use Case 1.
* Price targets\* are likely to be less than for the epidemic scenario Use Case, <$15 USD in the US, but considerably less in LMICs.
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| 1. Triage of non-symptomatic and symptomatic individuals in endemic settings
 | * The intended use is to determine if a symptomatic or non-symptomatic (asymptomatic or pre-symptomatic) person in an endemic setting has a reasonable likelihood of a current SARS-CoV-2 virus infection warranting temporary isolation pending confirmation testing.
* Confirmation testing is required and described in Use Case 4
 | * Same as above
 | * Same as Use Case 2
 | * While the sites for testing under this scenario are the same as for Use Cases 1 and 2, testing for non-symptomatic (pre-symptomatic and asymptomatic) individuals is far more difficult. Testing of the general population is problematic for a variety of reasons, including cost, access, awareness, appropriateness, logistics and others.
* This scenario could include non-symptomatic at-risk contacts of individuals who tested positive for SARS-CoV-2 virus infection.
* Anew symptomatic case will occasionally appear and could initiate a broader testing protocol for recent contacts.
* Decentralized testing is a preferred option for rapid turnaround, prevention of loss to follow-up and other reasons.
* In this case, using tests with very high sensitivity and specificity (>99%) could reduce or eliminate the need for confirmation testing. Individuals testing positive would be moved immediately to isolation. The large majority of individuals will be negative for COVID-19 (likely >99%). Such a triage test would be virtually indistinguishable from a diagnostic test in terms of performance, with the possible exception of cost and ease of use factors.
* False negative results are likely to result in new transmissions due to a false sense of safety in subjects told they are not infected but actually are. Models depicting these various testing scenarios have been reported and are being developed.
* The turnaround time should be maximally 1 hour, preferably 15 minutes or less
* For broadest utility, it is preferable that the test be CLIA-waivable for use by minimally trained users in decentralized testing settings
* See additional comments in Use Case 1.
* Price targets\* are likely to be <$25 USD in the US, with value premiums driven by the need to accurately and easily identify individuals early, and for convenience, but pricing pressure would remain in LMICs.
 |
| 1. Confirmatory of Triage testing
 | * The intended use is to confirm after triage testing that an individual is currently infected with SARS-CoV-2 virus
* Sites of testing would depend upon where the triage tests are being performed.
* In some situations, confirmation testing will be conducted at the same site as triage testing (same day), while in others testing could be a send-out test (multi-day)
* Tests used as diagnostics (Use Cases 5) are acceptable candidates for confirmation tests
 | * If respiratory tract samples are required, proper collection (e.g., nasal swab or saliva cup/tube) and sample introduction to testing device (e.g., swab introduction port) will be necessary
* Automated swab elution equipment may be required to support testing in high-volume settings
 | * Nasopharyngeal swabs remain a common choice for RNA tests, but there is a trend toward nasal sample types that are easier to collect such as nasal and mid-turbinate swabs. The latter options have been used in self-collection protocols with very good performance. The FDA no longer lists nasopharyngeal samples as the only preferred method.
* Saliva is becoming an acceptable alternative specimen but might be limited to samples with higher viral loads.
* Sputum and bronchial lavage specimens have use when testing for lower respiratory involvement.
* Feces and urine are not preferred specimen types, although, as opposed to urine, significant quantities of RNA have been detected in feces
* Sample types may be restricted to those validated for use with the highest performing assay technologies.
* Samples for confirmation testing could be different than for the triage test.
* It would be useful to have self-collection of samples with either courier pick up or shipment to testing sites for confirmation. This is being broadly instituted at the time of writing for saliva and nasal swabs for diagnostic testing
 | * For this use case, RNA tests are the most likely to be used (PCR, isothermal amplification, NGS). Depending upon their performance, antigen tests may also offer value
* It will be important to consider whether or not sufficient sample should be taken at the time of triage testing for potential use with a follow-up confirmatory test (if warranted), or if a second sample should be collected after results are obtained for the triage test. Taking a new second sample will be far easier in Group 1 sites than Group 2 sites (see Use Case 1) unless the confirmation test is available locally at the Group 2 site.
* In Group 2 sites, local confirmation testing is preferred, for instance, in a qualified lab near an emergency room or primary care facility.
* In Group 2 sites without local confirmation testing, it is probable that an individual will go home to self-isolate after a positive triage test. In this case, additional sample collection would be required if the confirmatory test is a send-out.
* Where confirmatory testing is not immediately available, the potential for loss to follow up must be considered in the case of the Group 2 sites
* On site turnaround of results <2 hours are preferred, but sooner would be better
* If send-out testing is required, delayed delivery of test results (several days) could result in unnecessary isolation.
* It is preferable that the test be CLIA-waivable for use by minimally trained users in decentralized testing settings, or CLIA moderately complex for use by laboratorians in small laboratories. However, shipment to large central labs is acceptable in some circumstance, such as Group 1 sites.
* If the triage testing is performed in settings with minimally trained personnel, careful thought should be given as to whether the confirmatory test could require a higher level of training or could be designed to accommodate sites with only minimally trained personnel available.
* Sensitivity and specificity targets are less stringent than for a diagnostic test, since after triage testing the population should be greatly enriched for infected persons. Existing diagnostic tests should prove adequate.
* In instances where the triage test has high enough performance, or when a diagnostic test is used for triage, the confirmatory test may not be required.
* Price targets\* are less stringent here where pricing could be up to $100 USD; lower in LMICs. Note that current reimbursement in the US ranges from $51 - $100 for non-CDC assays.
 |
| 1. Diagnosis of symptomatic individuals in endemic or epidemic settings
 | * The intended use is to diagnose a symptomatic individual with a SARS CoV-2 infection in an epidemic or endemic setting
* For use at the first healthcare site a patient or their contacts would enter to receive diagnosis and treatment
* Sites include primary healthcare facilities or where individuals are referred for advanced care, such as emergency rooms, urgent care clinics, and hospitals
* A positive test for SARS-CoV-2 virus or other epidemic-associated pathogens could trigger extra precautions, such as isolation, confirmatory testing, additional PPE, and contact follow-up, including healthcare staff
 | * Same as Use Case 4
 | * Same as Use Case 4, except for self-testing.
* It is useful to have self-collection of samples with either courier pick up or shipment to testing sites for testing.
 | * For this use case, RNA tests are the most likely to be used (PCR, isothermal amp, NGS).
* Antigen tests are becoming alternatives to RNA tests, but in special circumstances due to performance limitations. For instance, recent antigen tests receiving FDA EUA have limitations to the number of days after the onset of symptoms (5-12 days) when individuals would be tested. Thus far, non-symptomatic testing has not been approved, but several companies are pursuing the claim extension.
* Sensitivity and specificity need to be quite high (> 99%). A false negative result, particularly in at-risk populations (e.g., elderly or immunocompromised individuals), could result in a high morbidity and mortality rate, while also increasing the risk to medical personnel and increasing SARS-CoV-2 transmission.
* The performance of a confirmation test can be far below that of a diagnostic test because after triage testing the population will be greatly enriched for positive cases prior to confirmation. In contrast, the diagnostic test is used in a much broader population based on symptoms only. For instance, in a low prevalence setting of 0.1% the diagnostic test with a specificity of 99% would yield 10 false positive results to 1 true positive result. On the other hand, if the same population had been enriched by 100-fold during triage testing, a confirmation test with a 99% specificity would be acceptable.
* False positive results would lead to unnecessary and costly isolation or hospitalization. Also, healthcare personnel might be forced to wear extra PPE when it is not needed.
* Cross-reactivity with other respiratory and febrile pathogens and/or interfering substances would be highly problematic.
* The turnaround time should be maximally 1 hour, ideally 15 minutes or less in decentralized testing settings
* If off-site, send-out testing is required, delayed delivery of test results (several days, currently often 2-13 days) could impact the likely outcome of the person tested or result in unnecessary isolation.
* A test designed to meet the requirements for use in an endemic setting is also likely to meet the demands for an epidemic setting. One possible exception is the use of PPE, which is less likely to be used in full epidemic form in an endemic setting. If the diagnostic test is intended for use in both settings, consideration should be given to operator interface requirements for individuals wearing PPE. Subject self-collection of samples greatly decreases the need for PPE in the testing protocol.
* It is preferable that the test be CLIA-waivable for use by minimally trained users in decentralized testing settings, or CLIA moderately complex for use by laboratorians in small laboratories.
* Though current reimbursement in the US ranges from $51 - $100 for non-CDC assays, it is likely these amounts will fall with time. Price targets\* for a robust test could be up to $30 USD. Less in LMICs.
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| 1. Differential diagnosis in endemic or epidemic settings
 | * The intended use is to diagnose an individual with influenza like illness (e.g., Flu A/ B, RSV, SARS-CoV-2) in an endemic or epidemic setting
* It could be useful to also add common febrile disease pathogens, given the early clinical presentation of some COVID-19 patients (e.g., fever, aches, no respiratory symptoms)
* Differential testing could be applied in Use Cases 1, 2, 3, and 5
* For use at the first healthcare site a patient or their contacts would enter to receive diagnosis and treatment
* Sites include locations where individuals commonly present seeking primary care, such as emergency rooms, urgent care clinics, hospitals and primary healthcare facilities or where individuals are referred for advanced care
* A positive test for SARS-CoV-2 virus or other epidemic-associated pathogens could trigger extra precautions, such as isolation, confirmatory testing, additional PPE, and contact follow-up, including healthcare staff
 | * Same as Use Case 4
* For differential diagnostics, sample preparation can be a significant challenge. For example, pathogens that present in very low concentrations in the target sample may require additional steps such as culture, larger sample volumes, sample concentration, or other processes.
* It could be important to include additional pathogens to test. See comments.
 | * For standard respiratory pathogens such as influenza virus and RSV, nasal swabs are effective
* Sampling of the upper respiratory tract alone may not be a sufficient sample source for a differential diagnostic for other organisms since the optimum sample for one pathogen could be different for others. As a result, careful consideration must be given to appropriate samples and sample preparation requirements. However, respiratory pathogen panels are available using one common sample type.
* It is useful to have self-collection of samples with either courier pick up or shipment to testing sites for testing could be useful
 | * For this use case, RNA and DNA tests are the most likely to be used (PCR, isothermal amp, NGS). Depending upon their performance, antigen tests may also offer value, but this might not be true for all pathogens in a panel and could be more complicated to deploy than nucleic acid testing.
* Most of the individuals presenting to healthcare facilities with symptoms of respiratory or febrile illness are unlikely to have contracted COVID-19, even in epidemic settings. Possible exceptions could include elderly individuals from assisted living and skilled nursing facilities or other close human contact settings with known infections.
* Detection of other potential causative agents could provide healthcare workers with an immediate opportunity to treat and thus avoid further work up and postponement of treatment.
* Multiple pathogens could be present when viral infection leads to bacterial pneumonia or sepsis.
* If the test is designed to meet the higher performance requirements for endemic settings it should also be useful in epidemic settings with lower performance requirements.
* Determining whether upper or lower respiratory pathogens are indicated for testing is a critical consideration. Minimally the test would include SARS-CoV-2 and flu A/B detection capability. Depending on the region, time of year, and setting, other common respiratory pathogens might also be considered, such as RSV. Optimally, the test would include the other 4 coronaviruses associated with the upper respiratory infections and the common cold (HCoV 229E, NL63, OC43 and HKU1).
* Lower respiratory targets would include bacteria associated with pneumonia, bronchitis and potentially tuberculosis.
* Pathogens associated with febrile disease present more of a challenge based upon the geographic location of testing. Tests for fever of unknown origin may require different test methodologies (e.g., nucleic acid, immunoassay, chemistry) and samples.
* A single multiplex test designed to detect multiple pathogens from a single sample, or multiple tests (aka multi-parallel format), would be required. Multiple tests could be required to deal with multiple sample types needed.
* By referring either the sample or the patient for testing to other facilities, the test could be deployed at higher level infrastructure facilities to diagnose cases not possible to detect with existing technologies available at lower level centers; PPE use could vary from site to site.
* There could be additional clinical benefits to knowing that SARS-CoV-2 is a co-infection with other respiratory or febrile disease-causing pathogens, including shortened time to appropriate treatment, reduced risk of complications, reduction in health system crowding and reduced risk of disease transmission.
* There is a substantial challenge for developers to create multiplexed or multi-parallel tests with the necessary and sufficient performance for each target and, for multiplex tests, using a common sample type and sample preparation method. Nevertheless, a few SARS-CoV-2 tests combined with flu A/B have received FDA EUA.
* It is possible that in some situations it would be more useful to test for more common respiratory and febrile disease pathogens first, and then follow up with a differential diagnostic for other pathogens when a simpler cause was not found.
* A confirmatory test for all targets is not practical or necessary.
* If none of the pathogen targets of the differential diagnostic test are detected, it could be important to test for outbreak pathogens with major population health implications, such as new influenza strains, Lassa, Marburg, Ebola, SARS-CoV and MERS-CoV.
* Bio-threat pathogens are not considered here.
* Typically, instituting panel tests is cost prohibitive, although reports of inexpensive alternatives have appeared.
* In the event that there is a triage or disease severity test available that didn’t correlate with a specific pathogen (e.g., procalcitonin), then performing that test along with a differential diagnostic test could be a useful and successful approach.
* Price targets\* are somewhat higher than for a diagnostic test, in the $30-$120 USD range, depending on the number of targets included and the assay technology used. Less in LMICs.
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| 1. Previous SARS-CoV-2 exposure
 | * Intended for use to determine if an individual without symptoms has previously been exposed to SARS-CoV-2 virus.
* If the clinical data supports claims that exposure highly correlated with protective immunity, such an individual would not require isolation and could associate with uninfected or infected individuals with minimal danger of transmission or new infection.
 | * Can be performed with an ELISA or similar test format in a lab setting.
* A simple LFA or similar RDT format could be useful in some POC circumstances.
* For determination of immunity, a correlation between the specific reactivity with viral antigens (e.g., RBD, S1, S2, N) and antibody neutralization assays will be required.
* If antibody titer is required, the test would need to be quantitative
* Information and communications technologies (ICT) to capture and report data for reporting to other stakeholders is needed (e.g. healthcare workers, MOH, Public Health, CDC, WHO

  | * For an ELISA test, venipuncture blood is collected and shipped.
* For LFA tests, finger prick blood is preferred.
* Oral fluid is an alternative if antibody concentrations are high enough but would likely not be useful if a quantitative result is required.
 | * The tests are typically SARS-CoV-2 virus-specific IgA, IgM and/or IgG antibody detection assays. At this time IgG is the preferred immunoglobulin due to longer term (at least weeks) detection versus IgA and IgM. However, IgA and IgM can be useful for disease staging.
* Multiple virus proteins and protein segments are used for evaluation, including spike and nucleocapsid proteins. Inactivated virus isolates are also employed.
* Determining recency of infection can be helpful in determining whether an individual was previously infected with SARS-CoV-2 (e.g., IgA and IgM).
* Given the potential of transmission of the virus days after symptoms have ceased, it is possible that a viral clearance test (e.g., an RNA or potentially an antigen test) will be necessary in conjunction with an antibody test to determine that the infection has been resolved and the subject is no longer infectious.
* Since many people infected with SARS-CoV-2 are asymptomatic, tests of viral clearance of antibody positive persons are also potentially useful to determine that the subjects are not currently contagious
* It is probable that new tests will be necessary to provide test results that differentiate infectious from non-infectious RNA in clinical samples (e.g., genomic vs sub-genomic RNA fragments).
* It would be quite valuable to use properly designed tests to assess protective immunity (e.g., detection of epitopes associated with antibody viral neutralization assays).
* If immunity is temporary and the antibody clears after a few months, it might be necessary to measure the antibody titer. This approach would require that the effective titer is not too variable from person to person and that a test format is capable of delivering quantitative or semi-quantitative results.
* It is conceivable that it will be necessary to assess IgG subclasses.
* In the event that quantification of antibodies will be necessary, an ELISA (or equivalent) format may be easier to develop than a quantitative LFA or similar RDT.
* It could be useful to conduct serology studies in a cohort of convalescent patients to monitor antibody titers and immunity over time.
* Once vaccines are developed and widely used, there could become challenges to differentiating natural immunity from successful vaccination.
 |
| 1. Surveillance in sites of previous or potential outbreaks
 | * Intended use is to monitor a local or sentinel population for one of three purposes:

1) the estimation of incidence of current SARS-CoV-2 infection in symptomatic persons2) the estimation of incidence of current SARS-CoV-2 infection in non-symptomatic (asymptomatic and pre-symptomatic) persons 3) The estimation of prevalence of SARS-CoV-2 infection based upon prior exposure to SARS-CoV-2 * For intended use 1 and 2, it is possible that surveillance could constitute monitoring of testing conducted for diagnosis or screening without the need for new testing specifically for surveillance
* If SARS-CoV-2 diagnostics are not in routine use in the location of interest, procedures to test a statistically meaningful subset of the respiratory and febrile disease patient populations would be used.
* In addition, surveillance could be carried out in sentinel populations in higher risk situations than the general population in persons without symptoms (e.g., healthcare workers, first responders).
* Positive confirmation in a site of no or few previous infections would trigger a planned response.
 | * Use of multiplex assay technologies designed to detect more than one pathogen can be a convenient means of surveillance, provided test utility and cost match the target requirements.
* For RNA testing, it is probable that pooling of samples will be necessary to achieve cost goals.
* Molecular labeling (e.g., “bar coding”) of individual samples, in order to combine them for subsequent NGS analysis, followed by de-convolution, can be used to achieve pools of more than 100 samples. PCR amplification of the extracted samples to near equivalent concentration of the amplicons (library prep) is necessary.
* Remote, safe collection and transport of samples under secure conditions is required.
* For intended use 3 that requires serology tests, a confirmatory test using multiple antigens could be needed (e.g., western blot-like techniques), depending upon the configuration of the primary test and upon the prevalence of the population.
* ICT is needed for communication of results to stakeholders (e.g., healthcare workers, local governments, MOH, Public Health, CDC, WHO).
 | * The test must be developed to work with samples that are conveniently collected, such as nasal swabs, mid-turbinate swabs, saliva (RNA) and blood (serology)
* Use of nasopharyngeal swabs for surveillance would likely decrease the number of willing participants.
* Sample stabilization, deactivation and storage prior to safe shipment are important.
* Proper sealing of collection/shipment tubes is essential
* In some instances, surveillance may be accomplished via implementation of environmental monitoring (Use Case 9)
 | * There are two main types of testing questions that can be asked during a population surveillance study: 1) how many persons are currently infected (incidence)? and, 2) what portion of the population tested was previously infected (prevalence)? The former can be addressed with RNA testing, and possibly viral antigen testing. The latter can be addressed with immunoglobulin tests.
* Additional questions can be asked over time, such as: are the number of current infections changing (change in incidence)? Is the prevalence changing? Is the IgG titer decreasing? Over what period of time?
* Unfortunately, so far, the virus has not been routinely detected in blood (except in severe infections), so if RNA and immunoassay technologies are used, it could be necessary to use upper respiratory samples and blood samples, respectively.
* Immunoassays using upper respiratory samples for antigen and antibodies (e.g., secretory IgA) have also been developed.
* NGS would provide additional information concerning the genetic variation in SARS-CoV-2 over time and location.
* Where SARS-CoV-2 virus infection diagnostic testing is a routine part of respiratory and febrile disease diagnosis, a new surveillance test might not be necessary. Instead, only properly updated and deployed ICT is needed to report results in real time.
* If SARS-CoV-2 virus diagnostics are not routine, the determination of a new outbreak would require surveillance of some portion of the respiratory and febrile disease population, with the statistical sampling size to be determined.
* Turnaround time is important, but not critical.
* Specificity will be a significant issue, but it is possible that confirmation assays could be used after a presumptive positive, preferably to detect a different viral target molecule. RNA tests have had few false positives to date. Serology tests are more prone to false positive results, particularly in populations with less than 5% prevalence.
* Sensitivity should be high enough so that the results are indicative of the actual incidence or prevalence, depending on the intended use, in the tested population. Since the statistical power of a population study is very dependent upon the number of subjects tested, cost per sample is a major factor.
* For surveillance, it is not necessary to test all samples independently. Molecular labeling methods could make this approach economically feasible in NGS protocols. However, the low level of virus in early and late infection has resulted in concerns about the potential number of false negative results in pooled samples using PCR.
* ICT systems to alert key stakeholders, coupled to a planned response, would be essential.
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| 1. Environmental monitoring
 | * The intended use is to monitor for the presence of SARS-CoV-2 within a specific environment of interest
* The intended use is not detection of SARS-CoV-2 within infected persons
* Places to monitor the virus in the environment could include surfaces, air, water, latrines, or other sources of interest.
* Could be used in healthcare facilities, housing, businesses and other places of crowded occupation.
* Could be desirable to monitor the specific SARS-CoV-2 variant present to gain information concerning the source of contamination
 | * Sample collection, transport, elution, purification, concentration and other sample preparation steps are likely to be highly variable.
* Technology that collects and preserves target molecules will be required.
* It is possible that tests of viral RNA, protein or other components might not correlate with infectivity. Therefore, additional information could be required (e.g., intact RNA versus fragments or ability to culture virus).
 | * Given the potentially diverse sample types, collection devices and procedures, sample preparation methods can be quite different from other Use Cases (e.g., swabs of surfaces, latrine samples, water samples, air filters)
* Consideration should be given to how various sample collection media, sample and target analyte handling, transportation, storage, and stability considerations are handled.
* It is possible that many samples can be combined to decrease cost.
 | * Test results could be used to verify that sites where people gather are potentially free of SARS-CoV-2 virus contamination: healthcare facilities, assisted living sites, residential areas, food vendors, food processors, schools, restaurants, hotels, sports facilities, prisons, coffee shops, airplanes, rental cars and others.
* As opposed to testing each location or item over time, it could be far more practical and cost effective to validate the cleaning protocols.
* Cost targets would need to be quite low for any routine monitoring use, and higher for infrequent verification or process validation uses.
* Careful consideration is required for the processes to collect and store samples depending upon risk of contamination during sampling. Collection of air samples from city parks probably requires less personal protection than sampling hospital sewage.
* It is essential that test results are meaningful. It is possible that many reports to date of long virus persistence on surfaces will not correlate with the potential infectious nature of the viral sample. The test would be most valuable if the results could be compared to the *in vitro* cellular infectivity of the isolated virus-derived samples. This requirement for detecting infectivity will be a challenge for sample collection, preservation, and preparation to conduct the *in vitro* infectivity testing.
* Alternatively, it should be possible to show that the viral material collected is not composed of full-length viral RNA, which would imply that material is less likely to be infectious.
* If NGS is used for RNA analysis it could be possible to monitor the sequence variations in samples. This could be useful to determine the number of contamination events and/or the source of the contamination.
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| 1. Health Surveys and Health Checks
 | * The intended use is to screen persons for signs of SARS-CoV-2 infection within or prior to visiting a site of interest
* Some or all of the surveys or checks could be conducted at home prior to leaving for work, school or other occupied environments.
* The information can be used to determine the frequency of testing persons based on the risk of a recent infection
* Settings can include workplaces, residential sites, healthcare facilities, schools and others
 | * Devices for health checks, such as a non-contact thermometer, oximeters, “scratch and sniff” tests (for anosmia), pulse rate or others
* Devices for safely and remotely completing health surveys (e.g., smart phone apps, secure website)
* Questionnaires designed to assess risk for SARS-CoV-2 infection have been developed, tested in practice and implemented.
* Question sets have been devised by the CDC and others.
 | * None required or desired
 | * Prior to COVID-19, surveys have been shown to be effective tools in a variety of settings and disease states (e.g., for type 2 diabetes, multiple myeloma and volunteer blood donations).
* To be most effective, health surveys and checks should be highly sensitive so that few potential cases are missed, even at the risk of poor specificity. For instance, an American Diabetes Association questionnaire for assessing the likelihood that a person has type 2 diabetes is approximately 97% sensitive, but just 40% specific. A previous questionnaire with lower sensitivity and higher specificity was abandoned in favor of the improved sensitivity.
* Health surveys may be administered frequently, perhaps daily for all employees or students. Surveys can include questions such as: how are you feeling today, are you currently experiencing any of the following symptoms, have you been in contact during the last 14 days with anyone who has been diagnosed with SARS-CoV-2 virus infection, and other similar easy to complete questions. The answers can be used to determine the frequency of screening tests based on algorithms for pre-test probability of infection. These questionnaires can be studied in standard clinical trials with appropriate statistical designs (e.g., power, confidence levels).
* Workers’ rights regulations and privacy issues should be considered when constructing health survey and health check programs
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| 1. Screening of non-symptomatic persons
 | There are two intended uses: * 1) determine if a non-symptomatic individual (asymptomatic or pre-symptomatic) has a current SARS-CoV-2 infection
* 2) determine if an individual has been previously exposed and is likely to have temporary immunity to SARS-CoV-2 infection.
 | * For intended use 1, proper collection (e.g., nasal swab, saliva), sample processing (e.g., deactivation, sealing of collection device) and/or sample introduction to testing device (e.g., swab introduction port) will be necessary.
* For intended use 2, finger prick blood or potentially oral fluid is required with the test and will dictate test technology selection.
* The likelihood of immunity could require IgG titer determination
* It is possible that in order to assess the immunity of the person tested that multiple epitopes of the viral coat antigens will be required in the serology tests if they can be correlated with SARS-CoV-2 virus neutralization *in vitro* culture assays
 | * For intended use 1, the test is likely to be for RNA or antigen detection and must be developed to work with samples that are conveniently collected, such as nasal swabs, mid-turbinate swabs or saliva. Nasopharyngeal swabs are unlikely to be useful.
* For intended use 2, IgG is the most likely target. Finger prick blood is the preferred sample since the likelihood of detecting IgG is higher than in oral fluid.
 | * A key component of assessing the risk of returning to work or school is testing non-symptomatic individuals to isolate persons who are infected, don’t know it and are capable of transmission to others. It will also permit the positive person to seek appropriate care.
* Risk of infection is related to 1) living situation, 2) social interactions, 3) general health (e.g., pre-existing conditions), 4) work or school environment and 5) the general SARS-CoV-2 prevalence within the community in which the individual lives.
* This diversity of risk factors results in a broad pre-test probability of infection across the population base of interest. Testing protocols for employers or schools will likely require frequent testing until a means of knowing who to test more often than others is developed. Current models suggest that testing in 1-3-day intervals could be effective.
* To be useful, such a test must be inexpensive, easy to use, fast (less than 1 hour), broadly available and perform well (high PPV, acceptable NPV)
* Testing service options could include on-site, send-out and mobile labs. Selection will depend on the circumstances and needs of the particular healthcare system, employer or school.
* To be most effective, screening tests should be highly sensitive so that few potential cases are missed, even at the risk of poor specificity.
* Today, RNA testing is the most common test selection; however, antigen tests have been introduced that could have improved and acceptable performance. Recent EUA antigen tests have been shown to have high sensitivity in persons tested at 5-12 days after symptoms occur but have not been shown to be effective in non-symptomatic persons at the time of writing.
* Protocols for employee testing will be dependent upon the size of the workforce, whether it is a confined workforce with or without exposure to customers, local prevalence and other factors.
* Health surveys and checks could improve the efficiency and cost of testing algorithms and protocols.
* Intended use 2 will enable some portion of the workforce or student body to enter areas of potential exposure if the test indicates immunity, but this will be used for new students and employees and persons that have been infected, so will not be used often.
* Tests that can be used for this intended use have been developed using laboratory based neutralizing antibody tests, but these are expensive and not routine. Simple immunoassay tests that are correlated with neutralization assays are in development. It is not clear that viral neutralization *in vitro* is a true indicator of infectiousness.
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\*Price targets refers to the target price to the end user. This is a highly variable target, depending on the target use setting. Payments and reimbursement amounts are frequently influenced by the type of assay technology used. This may not be the complete price per result if other ancillary equipment or consumables are required. For health economic modeling, the complete price per result must be considered. Price targets should not be established relative to the current willingness to pay by governments and other users for SARS-CoV-2 tests during the early stages of the pandemic (e.g., $51 - $100 per test for non-CDC tests in the U.S.). Rather, price points should be targeted relative to other similar assay types currently on the market.