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USING PRE-TEST PROBABILITIES TO MORE EFFECTIVELY UTILIZE POINT-OF-CARE COVID-19 TESTING IN NURSING HOMES

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Abstract

Nursing home residents are at increased risk of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative infectious agent of COVID-19, as a result of exposure to asymptomatic or pre-symptomatic health care workers. In an effort to reopen nursing homes safely, federal agencies have proposed guidelines for testing of staff and residents at regular intervals. To mitigate testing shortages, facilities received antigen point-of-care (POC) testing devices for COVID-19 but without clear guidance on when to select an antigen vs. molecular based test and how to act on a positive or negative test result. This special article presents an algorithm for how to approach pre-test probability in the selection of a certain test and how to use post-test probability to act on a test result in the context of risk mitigation.

Introduction

The Centers for Medicare and Medicaid Services (CMS) has reported more than 368,000 confirmed or suspected COVID-19 resident cases and more than 55,800 COVID-19 resident deaths as of September 13, 2020 in US long-term care facilities.[1-3] Nursing home residents are at increased risk of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative infectious agent of COVID-19, as a result of exposure to asymptomatic or pre-symptomatic health care workers.[4-7] In an effort to reopen safely, CMS released phased reopening guidelines on May 18, 2020, instructing nursing homes to test staff and residents at regular intervals.[8, 9] In order to support these guidelines, CMS announced on July 14, 2020 that it would begin shipping rapid antigen testing supplies and kits to all long-term care facilities in the US.[10, 11]

As of August 20, 2020 the Office of the Assistant Secretary of Health (OASH) has arranged for approximately 14,200 facilities to receive either the Quidel Sofia® 2 Instrument or Becton, Dickinson and Company (BD) Veritor™ System by September 30, 2020.[12] Besides the staffing hours required to collect and process the specimens, the associated standard operating procedures and sample collection guidelines, and the need for a Clinical Laboratory Improvement Amendment (CLIA) Certificate of Waiver, long-term care providers and public health officials must determine how to properly select circumstances where an antigen test may be preferred and how to properly act on the results of the antigen test.

The Centers for Disease Control and Prevention (CDC) released updated interim guidance for rapid antigen testing for SARS-CoV-2 on August 16, 2020 defining diagnostic, screening, and surveillance testing and placing an increased emphasis on clinical intuition in selecting an appropriate test.[13] With the rapid distribution of antigen testing supplies and associated algorithms being updated, nursing homes must now quickly familiarize themselves with a re-emerging concept in biostatistics: pre-test and post-test probability. In a recent article, Woloshin and colleagues reviewed this concept in detail and concluded that even a negative result using a highly sensitivity test cannot rule out infection if the pre-test probability is greater than 33%.[14] As such, appropriate use of a simple algorithm to aid in selection of an appropriate use of antigen tests and interpretation of those results based on pre-test probability is important for nursing homes to understand.

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Screening or diagnostic testing: estimating pre-test probability

Being able to select the most appropriate test for a given clinical situation is a process clinicians practice every day. As a novel coronavirus, there was an initial delay in fast and reliable testing for COVID-19. In recent months, highly reliable and more affordable point-of-care (POC) antigen testing in nursing homes have become available. While the gold-standard for diagnosis of COVID-19 remains molecular testing such as the reverse transcriptase polymerase chain reaction (RT-PCR) based tests, POC antigen testing does have its utility.

The CDC guidance on diagnostic, screening, and surveillance algorithms lack details around determining the pre-test probability. Using the top of Table 1, pre-test probabilities can be estimated using 1) an estimate of the prevalence of disease in the cohort being analyzed, 2) the level of community transmission, and 3) the individual case presentation. High values in any category would increase the pre-test probability and move a person towards a diagnostic algorithm, on the right side of the table.

While this table contains common scenarios encountered in nursing homes, there are situations that may require more frequent testing of staff and/or residents. First, testing of asymptomatic staff, residents, surveyors, visitors, and vendors during a period of low community transmission (test positivity <5%) would utilize the Screening algorithm. Second, testing for purposes of contact tracing of residents/ or staff after identification of a possible exposure should trigger the use of the Screening algorithm with a low threshold for interval re-testing. Finally, testing during an outbreak investigation in which the pre-test probability is elevated may trigger a heightened level of awareness for false negatives. The Diagnostic algorithm should be reserved for situations during which the pre-test probability of COVID-19 is high (generally >10%) or the resident/staff is symptomatic.

Statistical performance of algorithms

It should be noted that while Table 2 lists sensitivities and specificities for the common antigen platforms on the market, these performance measures were determined in symptomatic residents. Based on early data in pre-symptomatic individuals, there could be a 67% false-negative rate on day 1 after exposure during the viral incubation period.[15] While there is no current data to guide the sensitivity of antigen testing in asymptomatic or presymptomatic individuals, viral counts have been similar in asymptomatic individuals giving hope to antigen tests for this population.[16, 17] To illustrate the concern over potentially lower sensitivities in this population, a hypothetical test situation has been included in Table 2 which lists 50% as the sensitivity and 98% for the specificity.

The screening algorithm when paired with a low pre-test probability (<10%) has a low negative post-test probability of less than 2% (see column 3 in Table 2). As such, in asymptomatic individuals, this may be enough justification for a "rule-out" approach as long as there is ongoing education regarding self-monitoring and appropriate screening criteria. The positive post-test probability is 98.8%-99.9% (see column 2 in Table 2) and may not be acceptable to "rule-in" disease where the psychosocial and cohorting practices pose high risk to the individual and even 1% false-positive rate may not be acceptable. While there is lack of data on sensitivity and specificity of asymptomatic individuals, based on the manufacturer guidelines, a positive should be considered presumed positive, require isolation in a Yellow zone or exclusion from work but should be confirmed with a molecular test prior to isolation in a Red Zone.

The diagnostic algorithm would aid clinical practice in the rapid confirmation of disease in individuals when there is a high pre-test probability of disease. As illustrated in Table 2, when the pre-test probability is 25%, the positive post-test probability is >99.96% and as such would not require confirmation with a molecular test. However, as stated previously, when the pre-test probability of disease is high, >30%, a negative test result does not rule out disease. For this reason, when the post-test probability remains high even after one negative test, it is advised to re-test an individual 2-5 days after onset of symptoms.

Interpretation of results

It has been advised that nursing homes in the United States maintain the capacity to care for individuals with COVID-19 for the foreseeable future. As such, each nursing home should maintain the flexibility to set up zones based on

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COVID-19 status. Green zones are asymptomatic individuals without concern for COVID-19 under no precautions. Yellow zones recent admissions or persons-under-investigation under isolation and precautions. Red zones refer to COVID-19 isolation units with dedicated entrance/exit areas for staff and confirmed COVID-19 residents. Acting on test results appropriately and isolating residents in these zones is a priority in Infection Prevention and Control (IPAC) practices (see Table 1).

Conclusion and implications

Development and rapid distribution of POC antigen tests for nursing homes is welcome but selection and interpretation guidelines have been vague to date. Outlined in this report is an algorithm and associated statistical analysis of positive and negative post-test probabilities that form a framework around how to think of the clinical utility of these tests. Future research should focus on the performance characteristics of antigen and molecular based tests in asymptomatic individuals and the value of simultaneous or repeated tests that may bolster the confidence in the results of a test.

Summary

Point-of-care antigen tests for COVID-19 are now widely available but without proper guidance. The algorithm presented here accounts for pre-test and post-test probability in interpretation of antigen testing results.

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All authors meet the four core criteria set forth by the International Committee of Medical Journal Editors (ICJME) for authorship.

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Tables and Figures

Table 1: Using Pretest Probability to Select an Appropriate Testing Algorithm[§§]: To use this table, review the estimated prevalence of the cohort being test, community metrics, and case presentation. In each of these rows, select the column with the appropriate answers and estimate the pre-test probability as low, medium, or high in row 4. Use the subsequent Screening or Diagnostic Algorithm and follow the guidance below the arrow for the results of the antigen testing with respect to confirmation, isolation, precautions, and zones.

	Pretest Probability			
Estimated Prevalence of Cohort	<1%	2-10%	>10%	
Community Metrics Test Positivity[*] Case Count[†] Hospitalizations[‡]	<5 % Declining Declining	5-10% No change No change	>10% Increasing Increasing	
Case Presentation Symptomatic[§] Exposure Risk[**]	No None	No Yes, with PPE[††]	Yes Yes, without PPE	
	LOW	**MEDIUM**	**HIGH**	
	⬇	⬇	⬇	
	Screening Algorithm		**Diagnostic Algorithm**	
	Antigen Test +	**Antigen Test -**	**Antigen Test +**	**Antigen Test -**
Confirm with RT-PCR Test	Yes	No	No	Yes
Isolation	Yes	No	Yes	Yes
Precautions	Droplet/ Contact	None	Droplet/ Contact	Droplet/ Contact
Zones[‡‡]	Yellow	Green	Red	Yellow

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*Test positivity: represents 7-day test positivity (molecular and antigen testing) by county.

†Case count: represents 7-day trend in case count by county.

‡Hospitalizations: represents 7-day trend in number of new hospitalizations by county.

§Symptomatic: A person with new unexplained symptoms of fevers (>100.0°F or subjective), chills, shortness of breath, fatigue, myalgias, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, or diarrhea.

**Exposure Risk: Per CDC, defined as prolonged (>15 minutes or during performance of aerosol generating procedure), close contact (being within 6 feet of person with confirmed COVID-19 or unprotected direct contact with infectious secretions or excretions of the person with confirmed COVID-19 OR 2) with a patient, visitor, or healthcare personnel with confirmed COVID-19.

††PPE(Personal Protective Equipment): gowns, gloves, mask, and goggles or faceshield.

‡‡Zones: 1) Green being asymptomatic residents without clinical suspicion for COVID-19, 2) Yellow being new admissions or persons under investigation (PUI) due to exposure/symptoms, 3) Red being COVID-19 Isolation Unit/Ward. Zones yellow and red require full gowns, gloves, mask, goggles/faceshield.

§§The table below describes recommendations for residents. Staff, visitors, vendors, and surveyors who test positive with an antigen test should not enter the building or continue to work until such time as they meet criteria for Return to Work. Staff who test positive but feel well enough to work may work on COVID-19 isolation unit. Assumes ample access to molecular and antigen based testing. If limited access to antigen testing, use molecular testing exclusively for Diagnostic Algorithm. If using molecular testing for Screening and Diagnostic Algorithm, no recommendations for confirmatory testing unless clinical suspicion remains high for active infection.

Table 2: Post-test Probabilities of Common Antigen Testing Platforms

Estimated Pre-test Probability (PTP)	**Positive Post-test Probability***	**Negative Post-test Probability†**
Quidel Sofia® SARS Antigen FIA (sensitivity: 96.7%, specificity: 99.99%, +LR‡ 9670, -LR§ 0.033)		
1%	98.99%	0.03%
5%	99.80%	0.17%
10%	99.91%	0.37%
25%	99.97%	1.09%
50%	99.99%	3.19%
BD Veritor™ System For Rapid Detection of SARS-CoV-2 (sensitivity: 83.9%, specificity: 99.99%, +LR‡ 8390, -LR§ 0.161)		
1%	98.83%	0.16%
5%	99.77%	0.84%
10%	99.89%	1.76%
25%	99.96%	5.09%
50%	99.99%	13.87%
Hypothetical System with Low Sensitivity (sensitivity: 50%, specificity: 98.0%, +LR‡ 25, -LR§ 0.510)		
1%	20.16%	0.51%

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5%	56.82%	2.62%
10%	73.53%	5.36%
25%	89.29%	14.53%
50%	96.15%	33.78%

*Positive Post-test Probability = ((PTP/(1-PTP))(+LR))/ [((PTP/(1-PTP))(+LR))+1]

†Negative Post-test Probability = ((PTP/(1-PTP))(-LR))/ [((PTP/(1-PTP))(-LR))+1]

‡+LR = Positive Likelihood Ratio = sensitivity / (1-specificity)

§-LR = Negative Likelihood Ratio = (1-sensitivity) / specificity