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COVID-19 antibody tests: statistical implications

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has had significant implications for society, with the introduction of restrictive social measures. Antibody tests provide a way of identifying patients who have been previously exposed to the virus and thus may have a degree of immunity. This is important in the development of public health policy, as local and national bodies seek to relax social restrictions in an attempt to mitigate the socioeconomic impact of the pandemic. This article explores the essential statistical concepts used to interpret the findings of diagnostic investigations, with examples illustrated using COVID-19 antibody tests.

Key words: Antibody; COVID-19; Pandemic; Predictive value; Sensitivity; Specificity

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has threatened the viability of international healthcare systems. During the initial stages of the pandemic, the principal focus was diagnosis with polymerase chain reaction nasal swab testing. As the basic reproduction number declined, the emphasis shifted to mass serological antibody testing (Eckerle and Meyer, 2020) to identify previous exposure to the pathogen. This can be used to establish the proportion of a population that has been infected (sero-prevalence), and in turn aid governmental decisions regarding the return to normal daily activities (Hall et al, 2020).

As antibody tests become widely available, the importance of having a diagnostically accurate serological test becomes paramount (Kumleben et al, 2020). Among healthcare professionals, shortcomings in the understanding of vital statistical concepts can lead to the misinterpretation of diagnostic tests. This article explores the application of statistical concepts and their implications for interpreting diagnostic test results, using COVID-19 antibody tests as an example.

Key statistical terms

In order to interpret the results of any diagnostic test, one must understand key statistical terms (Figure 1) and also be clear that no diagnostic test is perfect. Measures of accuracy (how close a measurement is to the true value) (Menditto et al, 2007) include sensitivity, specificity and predictive values (positive and negative). Sensitivity refers to the proportion of individuals with the disease who have a positive result, whereas specificity is the proportion of individuals without the disease who have a negative result. Of those testing positive, individuals with the disease are referred to as true positives and those without the disease as false positives. Similarly, of those testing negative, individuals without the disease are known as true negatives and those with the disease as false negatives.

The positive predictive value of a test refers to the proportion of positive tests that are true positives. The negative predictive value is the proportion of negative tests that are true negatives. The period prevalence refers to the proportion of people with the disease over a specified interval of time (Last, 2001). This includes existing, recovered and deceased cases. The period prevalence of COVID-19 is low because of the small number of cases relative to the size of the global population. It is important to note that as period prevalence increases, positive predictive value will increase while negative predictive value will decrease and as period prevalence decreases, positive predictive value will decrease while negative predictive value will increase (Akobeng, 2007).

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		Evidence of disease	
		Yes	No
Diagnostic test	Positive	True positive	False positive
	Negative	False negative	True negative

$$\text{Sensitivity} = \frac{\text{True positive}}{\text{True positive + false negative}} \times 100$$

$$\text{Specificity} = \frac{\text{True negative}}{\text{True negative + false positive}} \times 100$$

$$\text{Positive predictive value} = \frac{\text{True positive}}{\text{True positive + false positive}} \times 100$$

$$\text{Negative predictive value} = \frac{\text{True negative}}{\text{True negative + false negative}} \times 100$$

Figure 1. Formulae for key statistical terms.

Worked examples

The relatively low period prevalence of COVID-19 cases in the UK has a considerable impact on the positive predictive value and negative predictive value of both polymerase chain reaction and antibody tests for severe acute respiratory syndrome coronavirus 2. This article illustrates how the varying accuracy of an antibody test changes with the period prevalence of disease in a series of worked examples based on a model population of 10 000 people. The timing of a diagnostic test is crucial when interpreting results, as samples taken either too soon or late may lead to a greater false negative rate. More than 90% of individuals with polymerase chain reaction-confirmed COVID-19 are found to have detectable antibodies, peaking in the third week following symptom onset (Deeks et al, 2020). Thus, for the following worked examples, it is assumed that the antibody tests have been taken at the optimal time following exposure to COVID-19. As a caveat to the following examples, it is important to emphasise that any antibody test result acquires different significance depending upon context. For instance, an antibody test at the population level to ascertain seroprevalence is useful for informing policymakers, but how an antibody test on an individual basis may inform the behaviour of healthcare workers is quite different. Thus, the importance of the statistical measures of the test, such as sensitivity and specificity, varies according to the use of the test.

Worked example A (Figure 2) demonstrates that an antibody test with a sensitivity and specificity of 95%, in a population with 2% period prevalence of COVID-19, has a positive predictive value of 27.94% and negative predictive value of 99.89%. As the sensitivity is 95%, 190 people will correctly test positive for previous exposure to COVID-19, but 10 people will incorrectly test negative. As the specificity is 95%, 9310 people will correctly

An antibody test with a sensitivity of 95% and specificity of 95% in a population of 10 000 with a 2% period prevalence of COVID-19

		Evidence of previous infection	
		Yes	No
Antibody test	Positive	190	490
	Negative	10	9310

$$\text{Positive predictive value} = \frac{190}{190 + 490} \times 100 = 27.94\%$$

$$\text{Negative predictive value} = \frac{9310}{9310 + 10} \times 100 = 99.89\%$$

Figure 2. Worked example A.

An antibody test with a sensitivity of 99% and specificity of 99% in a population of 10 000 with a 2% period prevalence of COVID-19

		Evidence of previous infection	
		Yes	No
Antibody test	Positive	198	98
	Negative	2	9702

$$\text{Positive predictive value} = \frac{198}{198 + 98} \times 100 = 66.89\%$$

$$\text{Negative predictive value} = \frac{9702}{9702 + 2} \times 100 = 99.98\%$$

Figure 3. Worked example B.

An antibody test with a sensitivity of 95% and specificity of 5% in a population of 10 000 with a 40% period prevalence of COVID-19

		Evidence of previous infection	
		Yes	No
Antibody test	Positive	3960	60
	Negative	40	5940

$$\text{Positive predictive value} = \frac{3960}{3960 + 60} \times 100 = 98.51\%$$

$$\text{Negative predictive value} = \frac{5940}{5940 + 40} \times 100 = 99.33\%$$

Figure 4. Worked example C.

test negative for COVID-19, but 490 people will incorrectly test positive, despite having no antibodies. Of the 680 people who received positive test results, only 27.94% (190/190 + 490) truly had the disease, thus the probability of having COVID-19 after a positive result is low. Conversely, of the 9320 people who received negative test results, 99.89% (9310/9310 + 10) were truly negative, indicating that a negative test is more informative than a positive test in the context of a low period prevalence (Kumleben et al, 2020).

In worked example B (Figure 3), an antibody test with a sensitivity and specificity of 99% results in an increase in the positive predictive value from 27.94% to 66.89%. Despite a high sensitivity and specificity, when the period prevalence is as low as 2% in a population, antibody testing will inevitably yield a large number of false positives (Pinto da Costa et al, 2020), with a significant effect on the positive predictive value of the test.

The final worked example (Figure 4) considers an antibody test with a sensitivity and specificity of 99%, using a period prevalence of 40% of COVID-19. In a population of 10 000, of the 4020 people that tested positive, 98.51% (3960/3960 + 60) truly had COVID-19, resulting in a significant decrease in the false positive rate when compared to a population with lower period prevalence. The negative predictive value remains above 99%, signifying that the period prevalence has little effect on the negative predictive power.

Discussion

The base rate fallacy describes the cognitive error which commonly underlies the misinterpretation of antibody test results by clinicians or patients. Disproportionate weighting is often given to readily reported information such as high sensitivity and specificity values, without consideration of the period prevalence (Ohlert and Weißenberger, 2015). When the latter is acknowledged in conjunction with a positive test result, then one can better estimate the true level of population exposure.

Key points

- The introduction of mass serological testing for antibodies to severe acute respiratory syndrome coronavirus 2 could guide local and national bodies in devising policies to facilitate the return to normal daily activities.
- The understanding of key statistical concepts among healthcare professionals can avoid misinterpretation of antibody test results and diagnostic investigations both now and beyond this pandemic.
- The relatively low period prevalence of COVID-19 cases in the UK has a significant impact on the positive and negative predictive values of an antibody test.
- The concept of base rate fallacy, whereby less value is placed on the base rate of probability, highlights the importance of acknowledging the low period prevalence of COVID-19 when interpreting an antibody test.
- The long-term immunity acquired following exposure to COVID-19 has not yet been established.

The perceived low value of information that a positive antibody test gives has major implications when considering the clinical utility of the test. Importantly, a proportion of individuals with confirmed COVID-19 infection by polymerase chain reaction do not develop antibodies that can be detected by available antibody assays (Altman et al, 2020). Moreover, it remains unclear whether immunity against COVID-19 results from a previous infection. The form and longevity of any acquired immunity remains as yet opaque; if immunity does occur it is not known whether there is absolute immunity to a repeat infection or whether one's immune system simply acts to attenuate the pathological effect of such an event. Thus, interpreting the test results without consideration of these factors and the period prevalence may lead to an overestimation of the proportion of people who are supposedly 'immune' to COVID-19.

Conclusions

It is essential that one understands key statistical concepts when interpreting COVID-19 antibody tests and appreciates the limitations of the test, particularly the base rate fallacy phenomena. This can prevent misinterpretation of the accuracy of the test. A positive antibody test does not necessarily dictate that the individual has previously been infected with COVID-19, despite high sensitivity and specificity. All antibody tests require interpretation in context of the clinical picture. Furthermore, given the uncertainty surrounding immunity, there is an urgent need to determine the long term or transient nature of acquired immunity and whether reinfection is a possibility.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

References

Akobeng AK. Understanding diagnostic tests 1: sensitivity, specificity and predictive values. Acta Paediatr. 2007;96(3):338–341. https://doi.org/10.1111/j.1651-2227.2006.00180.x

Curriculum checklist

This article addresses the following requirements from the general internal medicine training curriculum

- Able to successfully function within NHS organisational and management systems.
- Is focussed on patient safety and delivers effective quality improvement in patient care.
- Carrying out research and managing data appropriately.

Altman D, Douek D, Boyton R. What policy makers need to know about COVID-19 protective immunity. Lancet. 2020;395(10236):1527–1529. https://doi.org/10.1016/S0140-6736(20)30985-5

Deeks JJ, Dinnes J, Takwoingi Y et al. Antibody tests for identification of current and past infection with SARS-CoV-2. Cochrane Database Syst Rev. 2020;6(6):CD013652. https://doi.org/10.1002/14651858.CD013652

Eckerle I, Meyer B. SARS-CoV-2 seroprevalence in COVID-19 hotspots. Lancet. 2020;396(10250):514–515. https://doi.org/10.1016/S0140-6736(20)31482-3

Hall MA, Studdert DM. Privileges and immunity certification during the COVID-19 pandemic. JAMA. 2020;323(22):2243–2244. https://doi.org/10.1001/jama.2020.7712

Kumleben N, Bhopal R, Czypionka T et al. Test, test, test for COVID-19 antibodies: the importance of sensitivity, specificity and predictive powers. Public Health. 2020;185:88–90. https://doi.org/10.1016/j.puhe.2020.06.006

Last J. A dictionary of epidemiology. Oxford: Oxford University Press; 2001

Menditto A, Patriarca M, Magnusson B. Understanding the meaning of accuracy, trueness and precision. Accred Qual Assur. 2007;12(1):45–47. https://doi.org/10.1007/s00769-006-0191-z

Ohlert C, Weißenberger B. Beating the base-rate fallacy: an experimental approach on the effectiveness of different information presentation formats. J Manag Control. 2015;26(1):51–80. https://doi.org/10.1007/s00187-015-0205-2

Pinto da Costa J, Barros H, Middleton J et al. COVID-19 testing: a reflection on test accuracy in the real world. 2020. https://www.aspher.org/download/420/covid-19_testing_a_reflection_on_test_accuracy_in_the_real_world.pdf (accessed 21 October 2020)