Is there value in a two-step diagnostic algorithm to confirm SARS-CoV-2 in South Africa?

To the Editor: SARS-CoV-2 molecular platforms that attained Food and Drug Administration Emergency Use Authorizations are currently being implemented worldwide.[1-4] These molecular platforms incorporate at least two gene targets, with positive percent agreements (PPA) of 95 - 100% and negative percent agreements (NPA) of 94 - 100%.[1-4] The South African (SA) Ministerial Advisory Group on COVID-19 recently outlined a mass screening programme involving a broadened case definition, active community surveillance and extensive contact tracing, with the aim of undertaking ~30 000 molecular SARS-CoV-2 screening tests daily in SA.[5]

We performed a hypothetical predictive study, using an average test prevalence of 3% (based on SA confirmed COVID-19-positive cases/total cases tested up to 22 April 2020)[6] and test PPA and NPA of 99%, taking into consideration possible pre-analytical and analytical confounders.[7] The positive predictive value (PPV) and negative predictive value (NPV) for SA were 75.4% and 99.9%, respectively. We also compared predictive values, using similar accuracy, of other countries that have implemented different testing and screening strategies (based on figures on 22 April 2020)[8,9] (Table 1).

Traditionally, for disease screening, a high NPV and sensitivity are ideal.[10] Given the current situation in SA, reporting false-positive SARS-CoV-2 cases may be justified based on facilitating social measures to contain the spread of the virus.[10] However, when disease prevalence is low, such as the current SA COVID-19 test prevalence of 3%, near-perfect specificity would be necessary to prevent false positives.[7] The prevention of false positives is particularly important when extensive contact tracing is instituted, where the appropriate use of resources is essential.[11,12] Other possible issues are legal implications due to infringement of freedom rights and loss of personal income due to self-isolation.[13]

Several solutions may decrease false positives when the test prevalence remains low, including:

- Performing reflex confirmatory molecular tests, using separate platforms with different targets, on screening positive samples. In our scenario, secondary confirmatory testing of positive samples, using a platform with similar accuracy, would increase the PPV to 99.7% (Table 1). However, confirmatory testing may delay contact tracing, depending on local testing capacity. Combined high-throughput screening and low-throughput confirmatory platforms may mitigate this. A cost-and-risk analysis comparing a single-test screening strategy and a two-step algorithm could be undertaken.

Table 1. A hypothetical two-step model to confirm SARS-CoV-2 in South Africa and comparison with other countries*

	True positive	True negative	Total
South Africa: test prevalence 3%			
Screening, *n*†			
Test positive	3 599	1 301	4 900
Test negative	36	128 838	128 874
Total	3 635	130 139	133 774
Confirmatory, *n*‡			
Test positive	3 658	12	3 670
Test negative	37	1 193	1 230
Total	3 695	1 205	4 900
South Korea: test prevalence 2%			
Screening, *n*§			
Test positive	10 587	5 281	15 868
Test negative	107	522 800	522 907
Total	10 694	528 081	538 775
Italy: test prevalence 12%			
Screening, *n*¶			
Test positive	185 454	13 227	198 681
Test negative	1 873	1 309 446	1 311 319
Total	187 327	1 322 673	1 510 000
USA: test prevalence 22%			
Screening, *n*‖			
Test positive	840 230	30 213	870 443
Test negative	8 487	2 991 070	2 999 557
Total	848 717	3 021 283	3 870 000
UK: test prevalence 24%			
Screening, *n***			
Test positive	132 160	4 264	136 424
Test negative	1 335	422 176	423 511
Total	133 495	426 440	559 935

PPV = positive predictive value; NPV = negative predictive value.
*Sensitivity and specificity of 99% were used for predictive calculations.
†PPV: 3 599/(3 599 + 1 301) = 75.4%, NPV: 128 838/(128 838 + 36) = 99.9%.
‡PPV: 3 658/(3 658 + 12) = 99.7%.
§PPV: 10 587/(10 587 + 5 281) = 66.7%, NPV: 522 800/(522 800 + 107) = 99.9%.
¶PPV: 185 454/(185 454 + 13 227) = 93.3%, NPV: 1 309 446/(1 309 446 + 1 873) = 99.9%.
‖PPV: 840 230/(840 230 + 30 213) = 96.6%, NPV: 2 991 070/(2 991 070 + 8 487) = 99.7%.
**PPV: 132 160/(132 160 + 4 264) = 96.9%, NPV: 422 176/(422 176 + 1 335) = 99.7%.

- Implementation of risk stratification based on disease grading, and only doing confirmatory tests on 'low'-risk cases (i.e. lower pre-test probability), may be more cost-effective but would be administratively challenging.
- Narrowing the case definition would improve the pre-test probability, but risks missing COVID-19 cases and minimises the benefits of the contact tracing programme.

We fully support the SA National Department of Health (NDoH) in expanding testing and contact tracing, and this letter is not intended as a criticism of the NDoH response, which has been widely praised. Our intention is to initiate discussion around the acknowledged challenges of mass screening and tracing programmes, and thereby, we hope, contribute in some way to the collective efforts in combating COVID-19 in SA. Consistent low test prevalence of SARS-CoV-2 might rationalise a two-step diagnostic algorithm to support cost-effective mass contact testing and tracing. A reference test standard remains lacking, and NPA values of current testing modalities highlight the need for further COVID-19 diagnostic accuracy studies.[1,2,4]

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