EPIDEMIOLOGIC PRIMER

GOAL: Provide the best testing advice to minimize the risk that a person infectious with SARS-CoV-2 could transmit the virus during travel and propose a testing regimen to minimize quarantine.

TERMINOLOGY:

		Disease status: Present	Disease status: Absent	
Screening test result	+	A	B	Total positive tests
	-	C	D	Total negative tests
		Total infected (Ti)	Total not infected (Tni)	Total population (Tp)

A: True Positives
B: False Positives
C: False Negatives
D: True Negatives

Prevalence. Disease burden, expressed as a percentage or rate with the total population as the denominator. Prevalence in this context refers to the number of existing cases of disease in a specified population at a given point in time.

Incidence. Number of new cases of disease in a specified population during a specified period of time.

Sensitivity. The likelihood that a test will correctly identify a person with the disease. A/(A+C) is the mathematical formula.

Specificity. The likelihood that a test will correctly identify a person without the disease. D/(B+D) is the mathematical formula.

Positive predictive value (PPV). How likely a positive test is a true positive. A/(A+B) is the mathematical formula.

Negative predictive value (NPV). How likely a negative test is true negative. D/(C+D) is the mathematical formula.

STEP ONE

Determine test performance requirements to maximize the number of people who could travel with reasonable certainty.

Prevalence assumptions/issues

1. It is important to know who might be infectious during travel as opposed to prevalence since the beginning of the outbreak. This is calculated by multiplying the incidence with the time period of infectiousness.

2. The Brown School of Public Health website is one of the best sites tracking the incidence or current new cases per 100 000 people: https://globalepidemics.org/key-metrics-for-covid-suppression/. However, it should be noted that some statistics might not be accurate due to limitations of testing and reporting systems.

3. Among those who are sick, the vast majority of people are infectious from two days prior to symptom onset to nine days following symptom onset; hence, 12 days are used to determine the time period where people could infect others.

4. The asymptomatic rate is assumed to be 40 per cent in accordance with a CDC reference published in July: https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html. This implies that 60 per cent of people are symptomatic. Further assuming that mainly symptomatic people get tested, the number of positive tests represents only 60 per cent of the total number of people who are potentially infectious.

Calculating prevalence

To calculate the prevalence of potentially infectious people with positive tests, use the Brown daily average of new cases per 100 000 people (a 7-day moving average; based on Assumption 2 above) and multiply it by 12 (the number of days a person might be infectious; based on Assumption 3 above).

Prevalence = incidence x duration
= number of people per 100 000 with positive tests x 12
= potentially infectious people with positive tests per 100 000 people

Taking into account that the number of positive tests represents only 60 per cent of the total number of people who are potentially infectious, the total number of potentially infectious people needs to be calculated. Setting the total number of people who might be potentially infectious as “X”, the number of people with positive tests must equal 0.6 times “X” (based on Assumption 3 above).

Potentially infectious people with positive tests = 0.6 x total number of potentially infectious people (“X”);
Total number of potentially infectious people (“X”) = Potentially infectious people with positive tests / 0.6

To calculate the prevalence percentage, divide “X” by 100 000 to get the ratio, then multiply it by 100 to get the percentage.

Prevalence percentage = ratio x 100
= “X” / 100 000 x 100
= x per cent

Example:

For State A, using the data from 21 September 2020 with a daily average of 12.6 per 100 000 people, the equations are as follows:

Prevalence = incidence x duration
= number of people per 100 000 with positive tests x 12
= 12.6 per 100 000 x 12
= 151.2 potentially infectious people with positive tests per 100 000 people

Potentially infectious people with positive tests = 0.6 x total number of potentially infectious people

Total number of potentially infectious people (X) = Potentially infectious people with positive tests / 0.6
= 151.2 per 100 000 / 0.6
= 252 per 100 000 people

Ratio = X / 100 000
= 252 / 100 000
= 0.00252

Prevalence percentage = 0.00252 x 100
= 0.252 per cent

Quick calculation of prevalence:
Because the only variable in this calculation that changes is the daily average, while all others are fixed, the whole calculation can be done by simply dividing the daily average per 100 000 people by 50. For example, State A with a daily average of new cases per 100 000 people of 12.6 has a prevalence of 12.6 / 50 = 0.252 per cent. It should be noted that this is only valid if the number of new cases is expressed per 100 000 people.

Performing the same functions for State B (7-day rolling average of 14.6/100 000) and State C (24.6/100 000 and the highest average on the Brown site) yields 0.292 and 0.492 per cent.

Performing 2 x 2 tables

— The tables were developed initially with the sensitivity and specificity of the most recent Emergency Use Agreement applications to the United States Food and Drug Administration (FDA) for the Abbot Rapid test (sensitivity of 97.1 per cent and specificity of 98.5 per cent).

— Then, the same prevalence values were run with the worst listed sensitivity (80 per cent) and specificity (92 per cent) on the John Hopkins' compendium of all COVID-19 tests currently approved.

— For additional comparison, the values for the poorest performing test were run using the highest prevalence in the United States County X.

— Finally, the tables were populated using the proposed sensitivity and specificity of 95 per cent.

— PCR testing typically has higher sensitivities and specificities and would have even higher performance.

Calculations used for the 2 x 2 tables

A quick reminder of the 2 x 2 table terminology:

Tp = the total number of people in the population
P = the prevalence as calculated above (daily average of new cases per 100 000 people divided by 50)
Ti = the total number of infected people in the population
Tni = the total number of people in the population who are not infected
A = the total number of people who are true positive
B = the total number of people who are false positive
C = the total number of people who are false negative
D = the total number of people who are true negative

The calculations are as follows:

P = daily average of new cases per 100 000 people / 50
Ti = A + C = Tp x P
Tni = B + D = Tp – Ti
Sensitivity = A / (A + C)
Specificity = D / (B + D)
PPV = A / (A + B)
NPV = D / (C + D)

(Prevalence of 10 per cent, sensitivity of 95 per cent, specificity of 95 per cent)

Step 1 — Using a population of 1 000, calculate the disease burden.

		Disease status: Present	Disease status: Absent	
Screening test result	+			
	-			
		100	900	1 000

1 000 x 0.10 = 100 with the disease

1 000 - 100 = 900 without the disease

Step 2 — Using sensitivity, calculate A (true +) and C (false -).

Disease status

Screening test result		Present	Absent	
	+	95		100 x 0.95 = 95 true positives
	-	5		100 - 95 = 5 false negatives
		100	900	1 000

Step 3 — Using specificity, calculate B (false +) and D (true -). Then, add up test positives and negatives.

Disease status

Screening test result		Present	Absent		
	+	95	45	140	900 x 0.95 = 855 true negatives
	-	5	855	860	900 - 855 = 45 false positives
		100	900	1 000	

Step 4 — Calculate the positive predictive value (PPV) and the negative predictive value (NPV).

PPV = true positives/test positives = (95/140) x 100 = 67.8 per cent

NPV = true negatives/all negatives = (855/860) x 100 = 99.4 per cent

Examples of calculations
(Varying prevalence, sensitivity and specificity)

Example 1

State A: Prevalence of 0.25 per cent, Abbott Emergency Use Authorized with a sensitivity of 97.1 per cent and a specificity of 98.5 per cent.

Disease status

Screening test result		Present	Absent	
	+	2 428	14 962	17 390
	-	72	982 538	982 610
		2 500	997 500	1 000 000

PPV = (2 428/17 390) x 100 = 14.0 per cent
NPV = (982 538/982 538) x 100 = 99.99 per cent

Example 2

State B: Prevalence of 0.292 per cent, Abbott Emergency Use Authorized with a sensitivity of 97.1 per cent and a specificity of 98.5 per cent.

Disease status

		Present	Absent	
Screening test result	+	2 835	14 956	17 791
	-	85	982 124	982 209
		2 920	997 080	1 000 000

PPV = (2 835/17 791) x 100 = 15.9 per cent
NPV = (982 124/982 209) x 100 = 99.99 per cent

Example 3

State C: Prevalence of 0.492 per cent, Abbott Emergency Use Authorized with a sensitivity of 97.1 per cent and a specificity of 98.5 per cent.

Disease status

		Present	Absent	
Screening test result	+	4 777	14 926	19 703
	-	143	982 154	980 297
		4 920	995 080	1 000 000

PPV = (4 777/19 703) x 100 = 24.2 per cent
NPV = (980 154/980 297) x 100 = 99.98 per cent

Example 4

State A: Prevalence of 0.25 per cent, worst case test with a sensitivity of 80 per cent and a specificity of 92 per cent.

Disease status

		Present	Absent	
Screening test result	+	2 000	79 800	81 800
	-	500	917 700	918 200
		2 500	997 500	1 000 000

PPV = (2 000/81 800) x 100 = 2.5 per cent
NPV = (917 700/918 200) x 100 = 99.94 per cent

Example 5

State B: Prevalence of 0.292 per cent, worst case test with a sensitivity of 80 per cent and a specificity of 92 per cent.

Disease status

		Present	Absent	
Screening test result	+	2 336	79 766	82 108
	-	584	917 314	917 898
		2 920	997 080	1 000 000

PPV = (2 336/82 108) x 100 = 2.8 per cent
NPV = (917 314/917 898) x 100 = 99.93 per cent

Example 6

State C: Prevalence of 0.492 per cent, worst case test with a sensitivity of 80 per cent and a specificity of 92 per cent.

Disease status

		Present	Absent	
Screening test result	+	3 936	79 606	83 542
	-	984	915 474	916 458
		4 920	995 080	1 000 000

PPV = (3 936/83 542) x 100 = 4.7 per cent
NPV = (915 474/916 458) x 100 = 99.89 per cent

Example 7

County X: Prevalence of 5.994 per cent, worst case test with a sensitivity of 80 per cent and a specificity of 92 per cent.

Disease status

		Present	Absent	
Screening test result	+	47 952	75 208	123 157
	-	11 988	864 855	876 843
		59 940	940 060	1 000 000

PPV = (47 952/123 157) x 100 = 38.9 per cent
NPV = (864 855/876 843) x 100 = 98.6 per cent

Example 8

State A: Prevalence of 0.25 per cent, worst case test with a sensitivity of 95 per cent and a specificity of 95 per cent.

Disease status

Screening test result	Present	Absent	
+	2 375	50 000	52 375
-	125	947 625	947 750
	2 500	997 500	1 000 000

PPV = (2 375/52 375) x 100 = 4.75 per cent, or only 1 out of approximately 20 will be a true positive.
NPV = (947 625/947 750) x 100 = 99.99 per cent, or 1 in approximately 10 000 testing negative might be positive.

Example 9

State B: Prevalence of 0.292 per cent, worst case test with a sensitivity of 95 per cent and a specificity of 95 per cent.

Disease status

Screening test result	Present	Absent	
+	2 774	49 854	52 628
-	146	947 226	947 372
	2 920	997 080	1 000 000

PPV = (2 774/52 628) x 100 = 5.27 per cent, or only 1 out of approximately 20 will be a true positive.
NPV = (947 226/947 372) x 100 = 99.98 per cent, or 1 in approximately 10 000 testing negative might be positive.

Example 10

State C: Prevalence of 0.492 per cent, worst case test with a sensitivity of 95 per cent and a specificity of 95 per cent.

Disease status

Screening test result	Present	Absent	
+	4 674	49 754	54 428
-	246	945 326	945 572
	4 920	995 080	1 000 000

PPV = (4 674/54 428) x 100 = 8.59 per cent, or nearly 1 out of 10 will be a true positive.
NPV = (945 326/945 572) x 100 = 99.97 per cent, or 1 in approximately 5 000 testing negative might be positive.

Example 11

County X: Prevalence of 5.994 per cent, worst case test with a sensitivity of 95 per cent and a specificity of 95 per cent.

Disease status

		Present	Absent	
Screening test result	+	56 943	48 003	103 946
	-	2 997	893 057	896 054
		59 940	940 060	1 000 000

PPV = (56 943/103 946) x 100 = 54.78 per cent, or slightly over 1 out of 2 will be a true positive.
NPV = (893 057/896 054) x 100 = 99.67 per cent, or 1 in approximately 300 with a negative test might be positive.

Notes:

1.— The prevalence does not affect the performance of the test with respect to the sensitivity and specificity. It affects the number of infected and uninfected persons in a cohort of people.

2.— As prevalence goes up when performing a screening test, so does the positive predictive value.

3.— In a low prevalence situation, the negative predictive value is very little affected by even relatively poor performing tests.

4.— Poor performing tests will significantly increase the number of false positives who would be denied boarding, at least initially until confirmatory test can be completed.

Justifications for setting the minimum sensitivity and specificity levels at 95 per cent

1. It will allow a wider range of test devices to be used that are currently fielded as opposed to forcing States to procure newer models that are frequently hard to obtain.

2. The wider range also allows for the use of rapid antigen tests as a screening device which are more accessible and practical for application in the aviation environment; which are much faster and less expensive to use. In addition, it would reserve the more expensive real-time RT-PCR tests for confirmation of positives in conjunction with clinical correlation.

3. Setting the specificity at 95 per cent maintains a high NPV and reduces the false positives.

4. Setting the sensitivity at 95 per cent will reduce the risk of false negatives and improve the PPV.

5. In low prevalence settings (equating to 10-25 cases per 100 000 on a rolling average), the NPV equates to mislabelling an infected person as negative between 1 in 5 000 and 10 000 negative tests. In higher prevalence settings (equating to over 50 cases per 100 000 on a rolling average), the mislabelling rises close to 1 in 300.

6. In the same low prevalence and higher prevalence range, the PPV improves from correctly labelling a positive from approximately 1 in 10 to 20, to slightly better than 1 out of 2 of positive tests.

7. Few States set their sensitivity and specificity higher leading to further improvements in test performance.

STEP TWO: Pre-departure testing interval

Assumptions

— Incubation time: 2-12 days (95 per cent) with a medial of 5-6 days.

— Shedding can occur 48 hours prior.

— The most sensitive tests turn positive 1-3 days prior to symptoms.

— Leaving a 2- to 4-day period where a person could be infected but not infectious with a negative test.

— The goal is to limit infectivity in flight.

Considerations

1. If the testing is placed at 72 hours before their departure, at least 60 per cent of those infected with a negative test will manifest their illness and hopefully remove themselves from travel even if they were infected walking into the testing facility.

2. If the person with a negative test is a true negative and becomes infected walking out of the testing facility, they should not begin shedding the virus in most cases until after arrival at the destination.

3. Moving testing to 48 hours prior to departure would potentially let a few more of the negative but infected slip through who could begin shedding the virus in flight before developing symptoms, but would increase the likelihood that a person subsequently infected would not become infectious in flight.

STEP THREE: Can quarantine be reduced with serial testing?

Considerations

Consideration was given to two studies from the United Kingdom examining the relative effectiveness of various health measures on arrival to reduce the potential for onward transmission. It is summarized below:

- Quarantine of 14 days (Gold Standard): 78-99 per cent effective
- Single RT-PCR upon arrival: 39.6 per cent effective (2 in 5 cases detected)
- Single RT-PCR at 4 days after arrival: 64.3 per cent effective
- Single RT-PCR at 5 days after arrival: 88 per cent effective
- Upon arrival and 4 days after arrival (two tests): 68.9 per cent effective
- Single RT-PCR at 7 days after arrival: 94 per cent effective

Discussion

1. Assuming the effective percentages are the ability to find the people who could transmit the disease after release from quarantine, it seems reasonable to say that a 5 or 7-day window prevents most of the subsequent transmigration of disease.

2. The question is whether testing 72 hours prior to arrival, with a second test on day 4 or 5, would approach the 94 per cent effectiveness described for a single TR-PCR test 7 days after arrival.

3. Logically, it would appear a 7-day window of proven negativity would provide the same level of effectiveness.

Notes for consideration

1.— In the screening environment, the exact test is not as important as the technique in conjunction with the sensitivity and specificity. The sensitivity and specificity should be of at least 95 per cent and performed by people adequately trained using the techniques specified by the manufacturer. Laboratory certification is preferred.

2.— Evaluation of the positive cases must be considered.

3.— With the level of prevalence in various States, the PPV with the best tests available are going to be in the 10 to 25 per cent range, meaning 1 in 4 to 10 will be true positives.

4.— The other 75 to 90 per cent will be false positives and denied boarding.

5.— If less sensitive and specific tests are used for screening, the numbers go up significantly to as many 24 out of 25 positive tests being false positives.

6.— Furthermore, some of the true positives may be shedding viral remnants and no longer be infectious and could therefore travel.

7.— Clinical correlation and more definitive testing will be required in case of positive screening test results.

8.— States should consider what form would be acceptable to declare someone with a positive test as not infectious and ready to travel.

— END —