SARS-COV-2 TESTING

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ACCURACY OF SARS-2 TEST:

-GETTING THE RIGHT RESULTS AT THE RIGHT TIME
-TIPS ON ORDERING AND INTERPRETING SARS-COV-2

	Disease or condition status	
	Subjects with disease (D+)	Subjects without disease (D-)
Test Positive (T+)	True Positive (TP)	False Positive (FP)
Test Negative (T-)	False Negative (FN)	True Negative (TN)

Sensitivity
TP/(TP+FN)

Probability of T+/D+

Specificity
TN/(FP+TN)

Probability of T-/D-

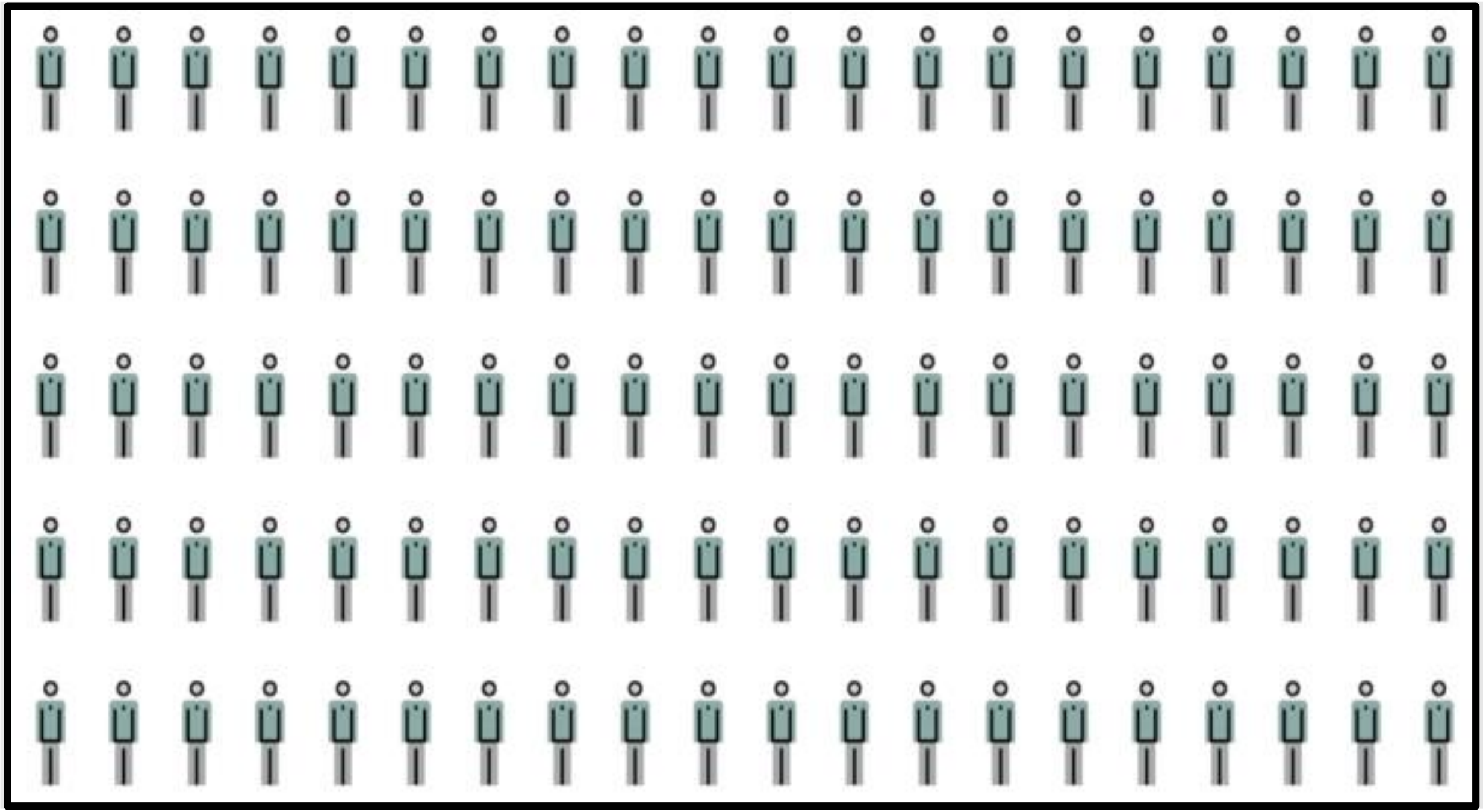
Probability of D+/T+

Positive Predictive Value (PPV)
TP/(TP+FP)

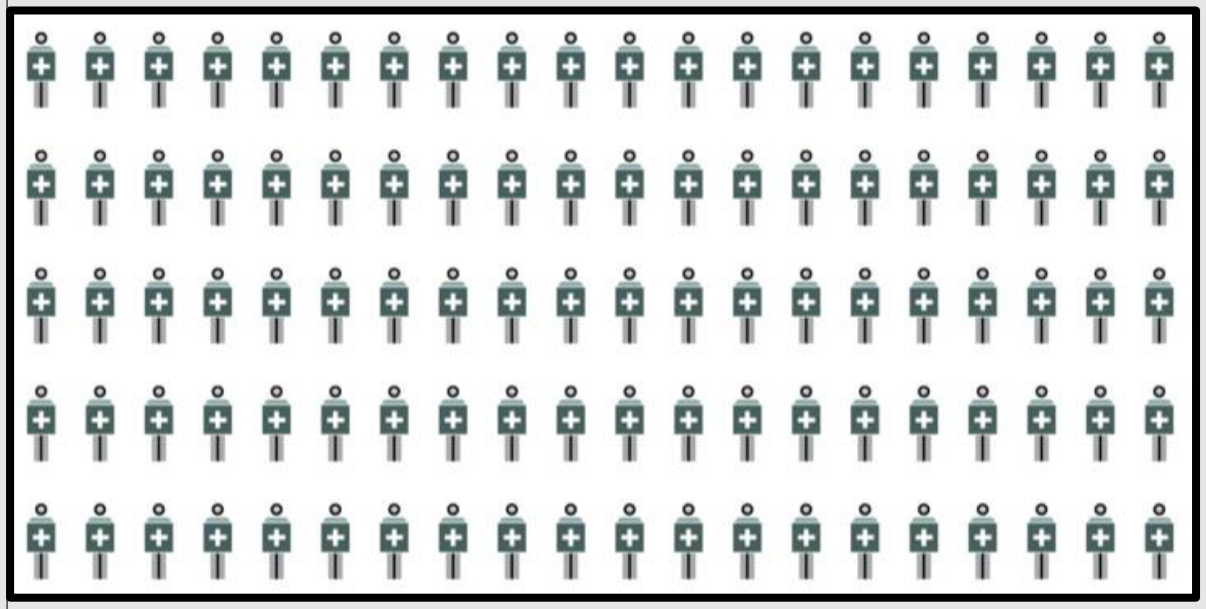
Negative Predictive Value (PPV)
TN/(FN+TN)

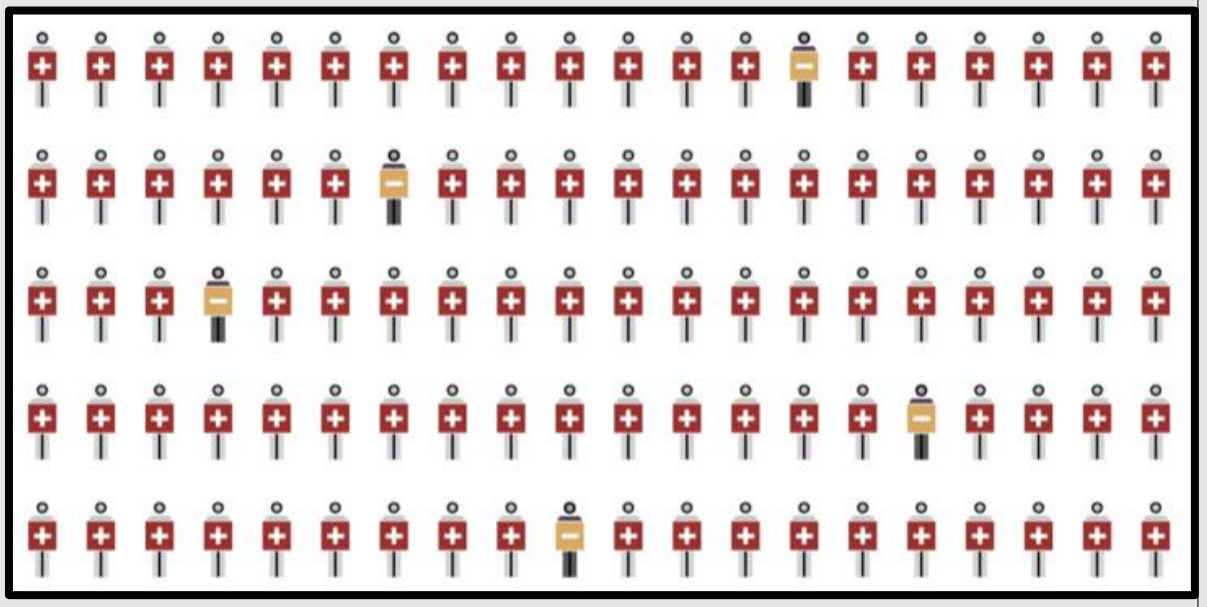
Probability of D-/T-

Accuracy
(TP+TN)/(TP+FP+FN+TN)



Sensitivity of the test: 100 people with antibodies

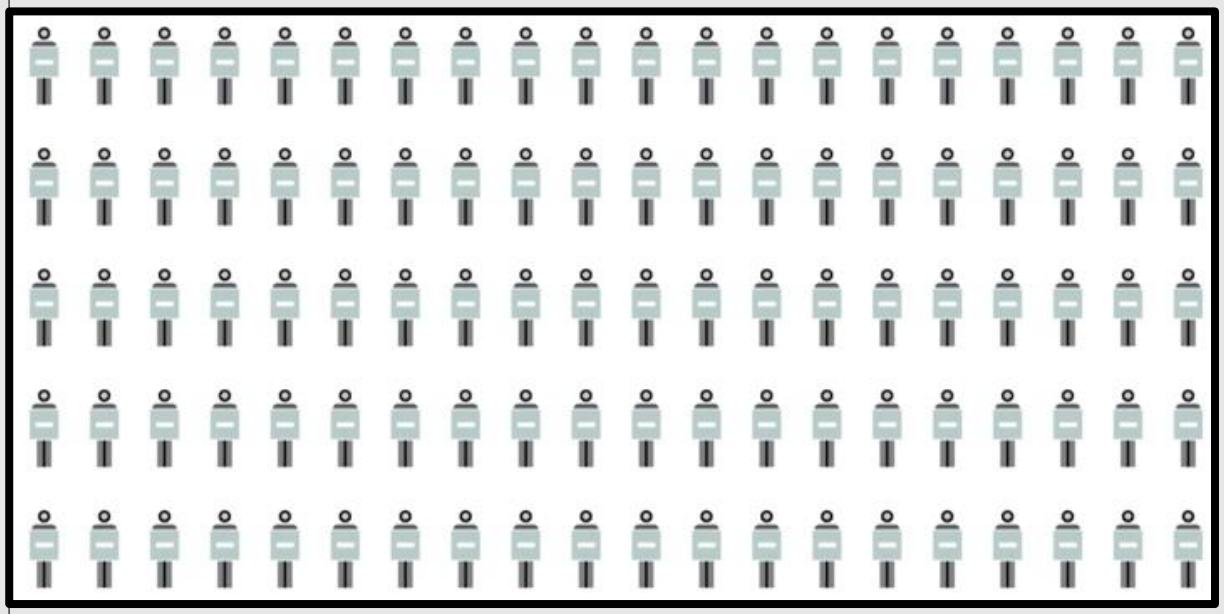




95 True Positives
5 False Negatives

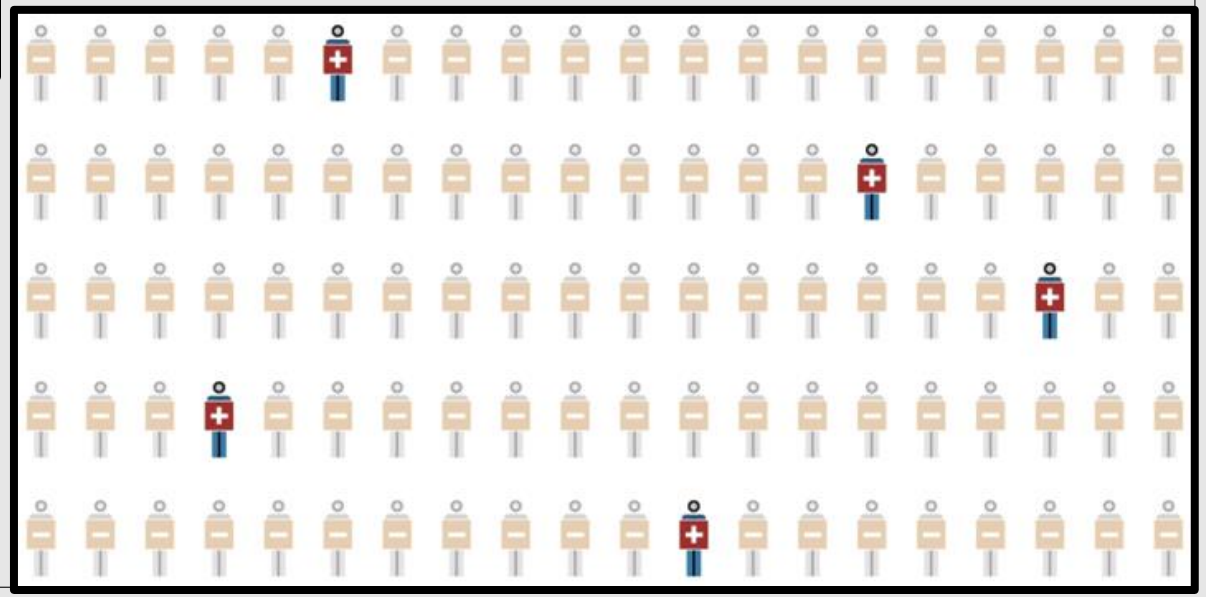
Sensitivity
TP/(TP+FN)

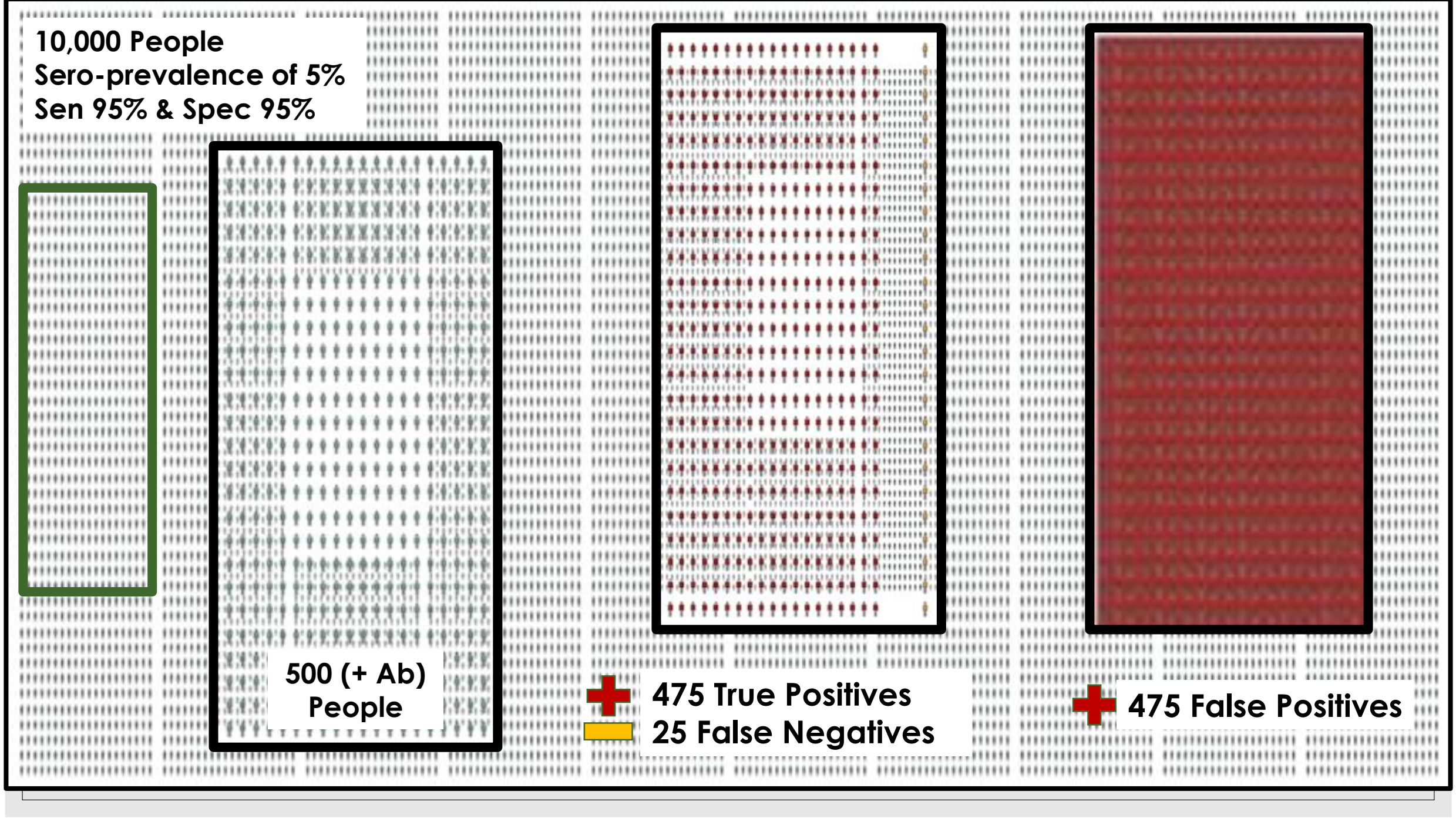
Specificity of the test: 100 people without antibodies

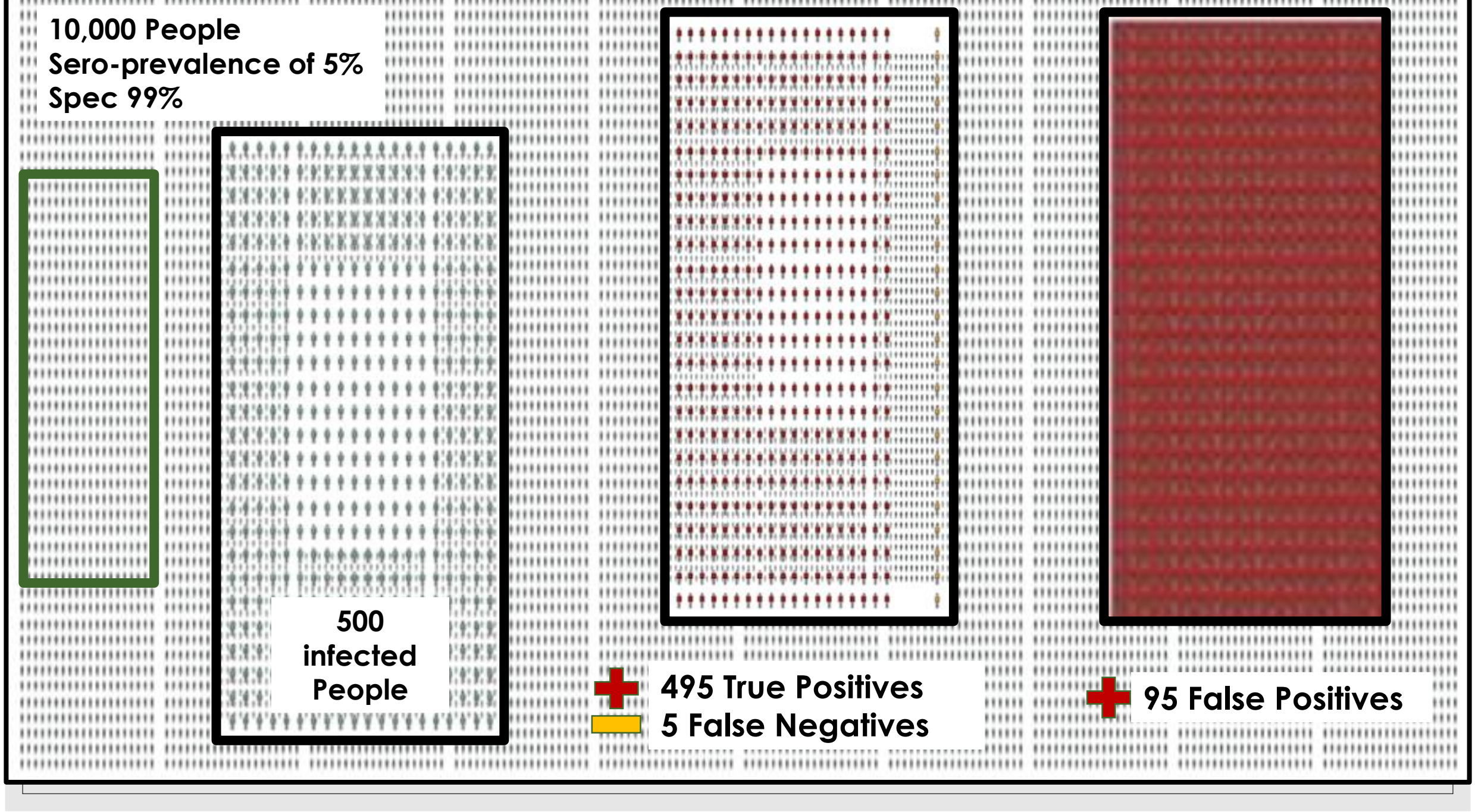


5 False Positives
95 True Negatives

Specificity
TN/(FP+TN)

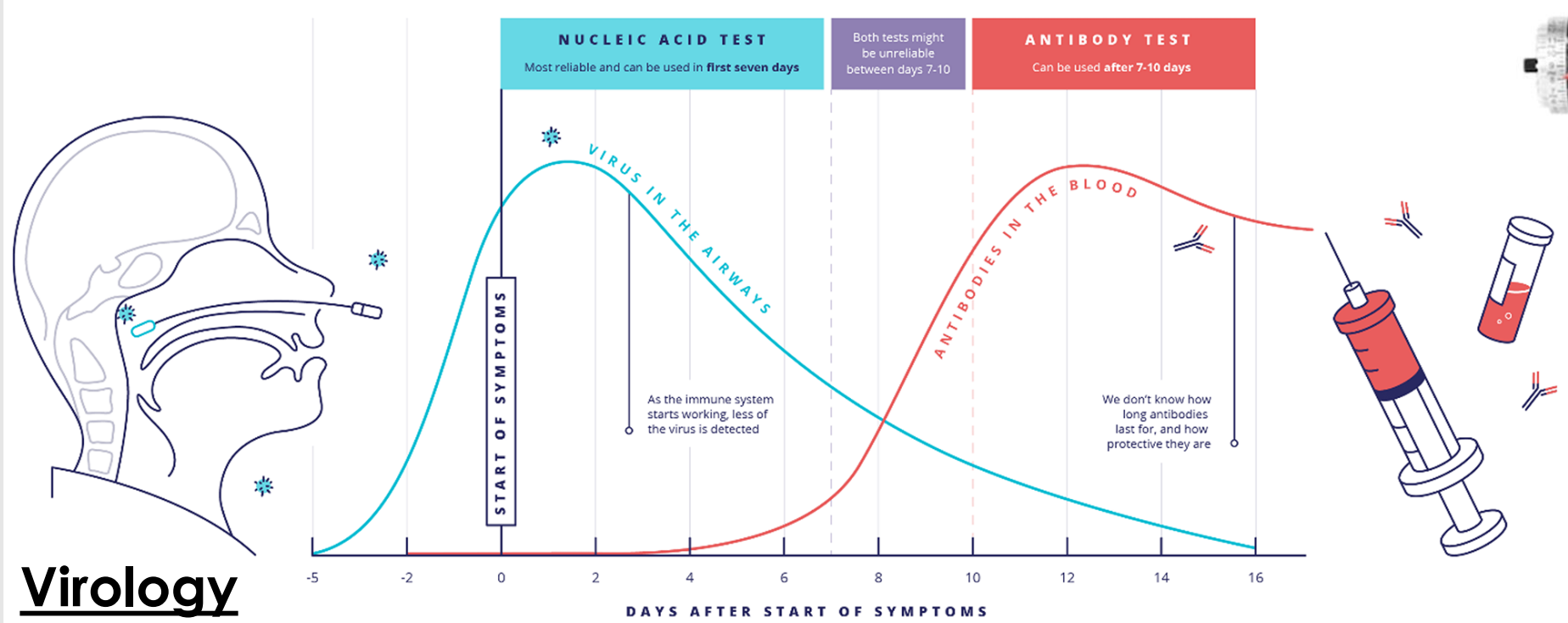


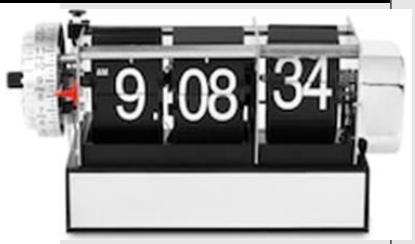

10,000 People
Sero-prevalence of 5%
Sen 95% & Spec 95%
500 (+ Ab) People
475 True Positives
25 False Negatives
475 False Positives


10,000 People
Sero-prevalence of 5%
Spec 99%
500
infected
People
495 True Positives
5 False Negatives
95 False Positives

TESTING

SARS-CoV-2 surveillance/diagnosis: What is the best approach?





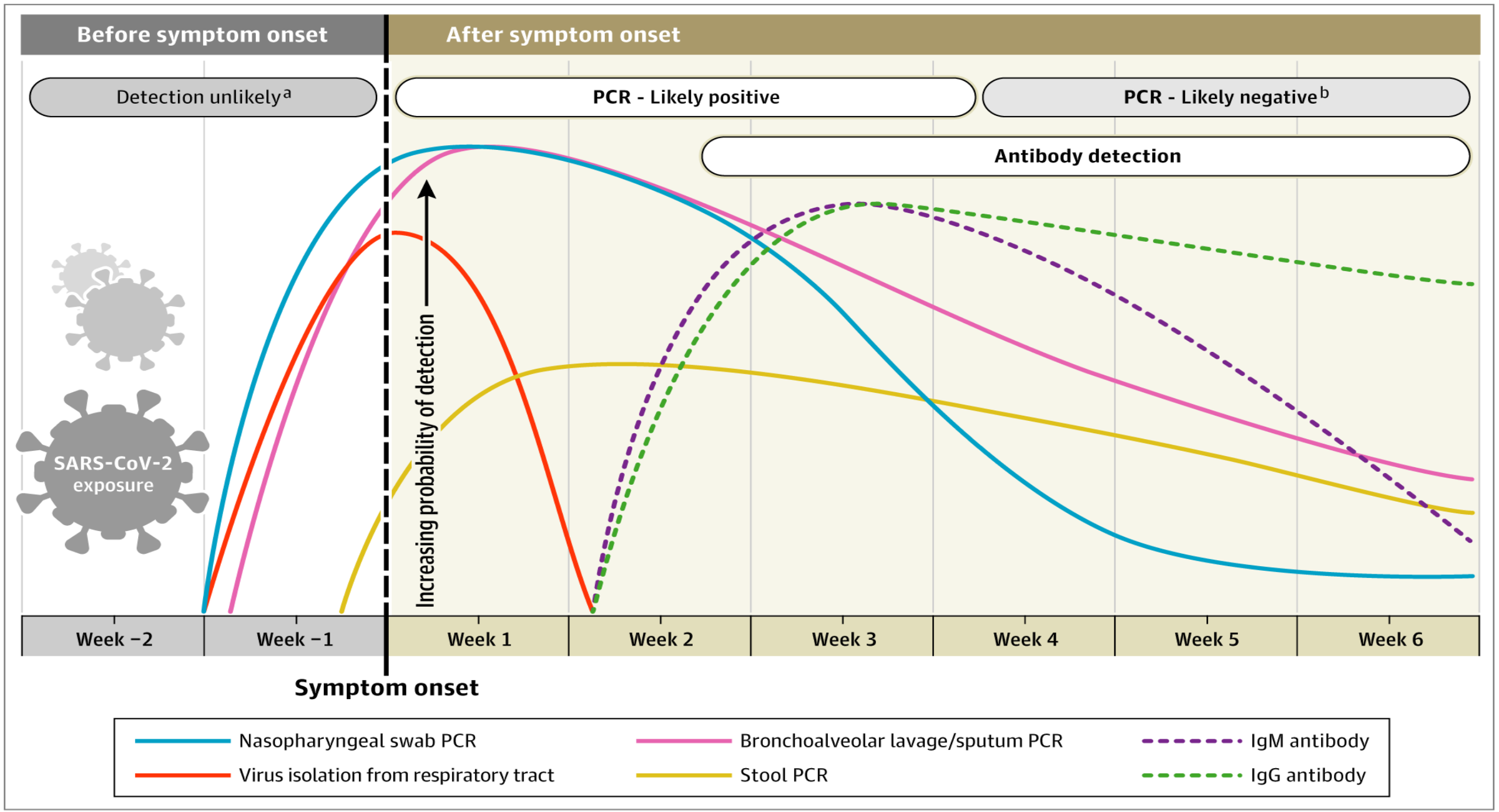
Virology

- It detects cases here and now
- Find, isolate, contact trace, quarantine
- Transiently positive 1-3 weeks
- High sensitivity for individual infection
- Miss many individuals if test late

Serology

- Positive 1-2 weeks after exposure
- Positive for months
- Higher sensitivity for population transmission
- Powerful for surveillance programs

Wölfel R, et al. Virological assessment of hospitalized patients with COVID-19. Nature 2020.;581(7809):465-469.



Sethuraman S, et al. Interpreting Diagnostic Tests for SARS-CoV-2. *JAMA.* 2020;323(22):2249-2251.

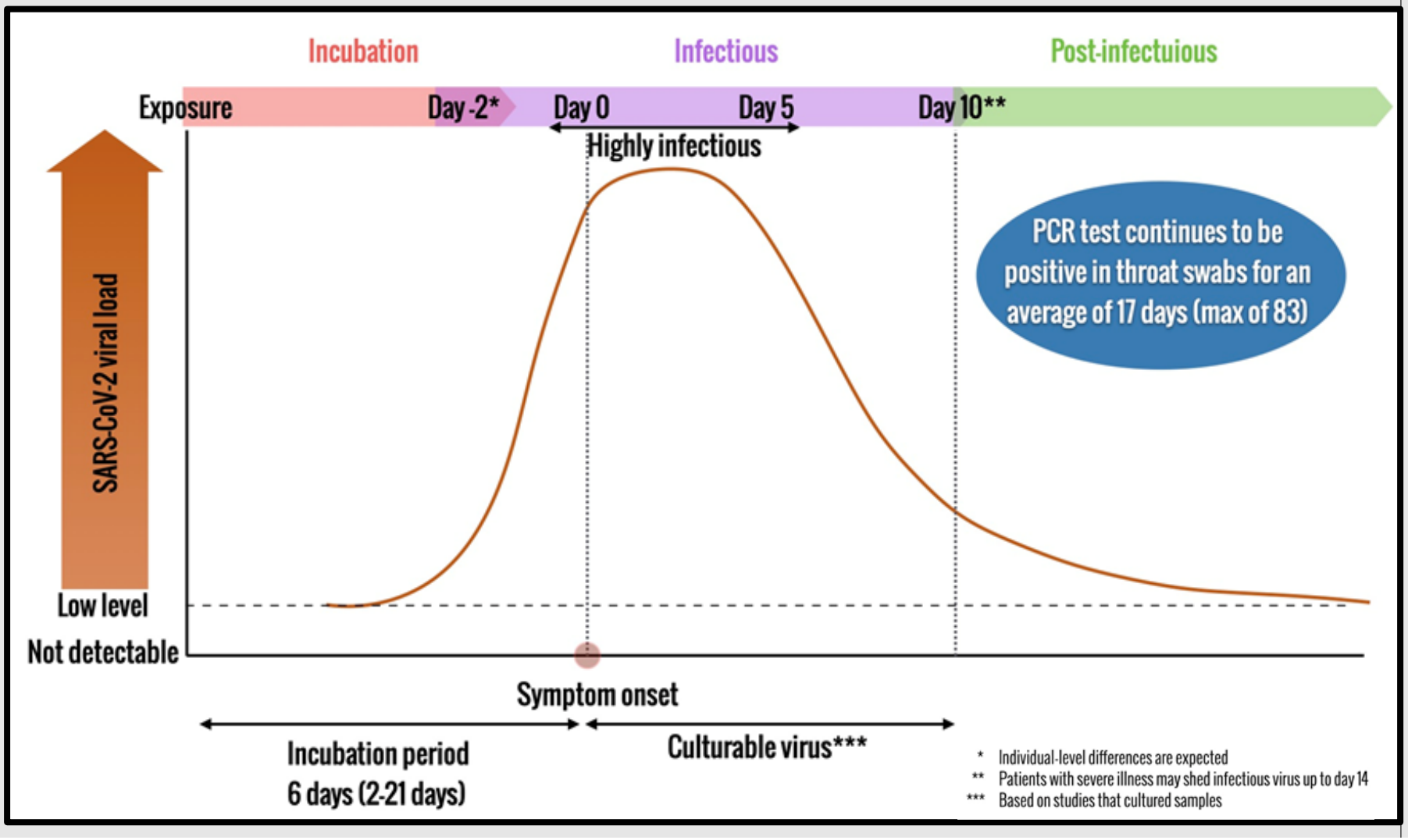
SARS-CoV-2 Serology for Diagnosis: Current Recommendations

- CDC: Given that it can take 1-3 wks to develop antibodies following infection, antibody test results should not be used to diagnose someone with an active SARS-CoV-2 infection[1]
- Royal College of Pathologists of Australasia[2]:
  - *"Molecular testing on a single throat with deep nasal swab is the current test of choice for the diagnosis of acute COVID-19 infection"*
  - *"COVID-19 IgG/IgM rapid tests have no role to play in the acute diagnosis of COVID-19 virus infection . . ."*
  - *"COVID-19 IgG/IgM rapid tests will miss patients in early stages of disease when they are infectious to other people"*
- WHO: *"At present, based on current evidence, WHO recommends the use of these new point-of-care immunodiagnostic tests only in research settings"*[3]

1. https://www.cdc.gov/coronavirus/2019-ncov/lab/serology-testing.html.
2. https://www.rcpa.edu.au/getattachment/bf9c7996-6467-44e6-81f2-e2e0cd71a4c7/COVID19-IgG-IgM-RAPID-POCT-TESTS.aspx.
3. https://www.who.int/news-room/commentaries/detail/advice-on-the-use-of-point-of-care-immunodiagnostic-tests-for-covid-19.

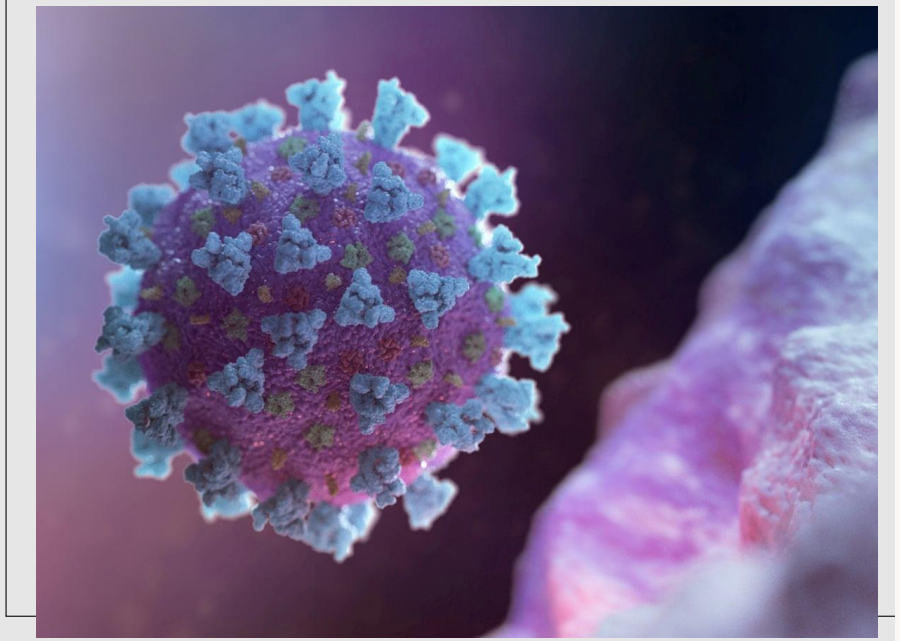
Can we use testing to control pandemics??

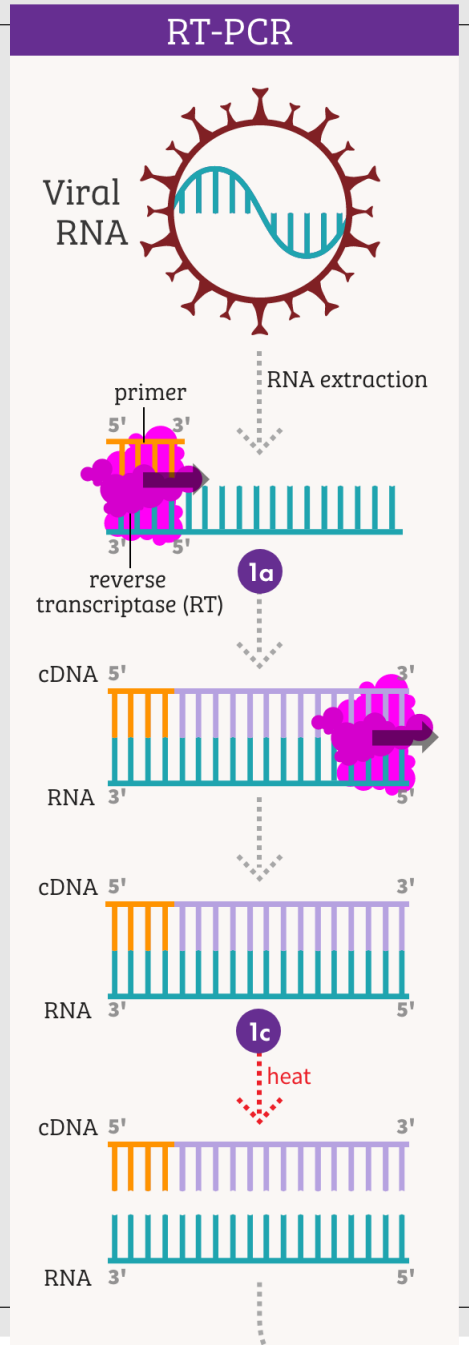
SARS-CoV-2 viral load dynamics, duration of viral shedding and infectiousness

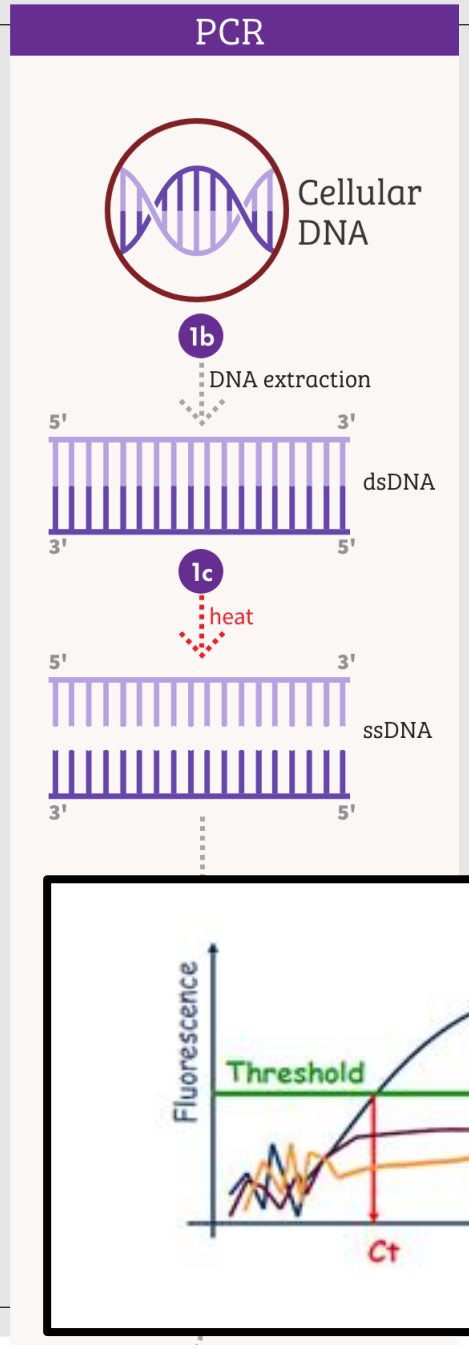


Cevik M, et al. SARS-CoV-2, SARS-CoV-1 and MERS-CoV viral load dynamics, duration of viral shedding and infectiousness: a living systematic review and meta-analysis. MedRxiv (2020). doi: https://doi.org/10.1101/2020.07.25.20162107

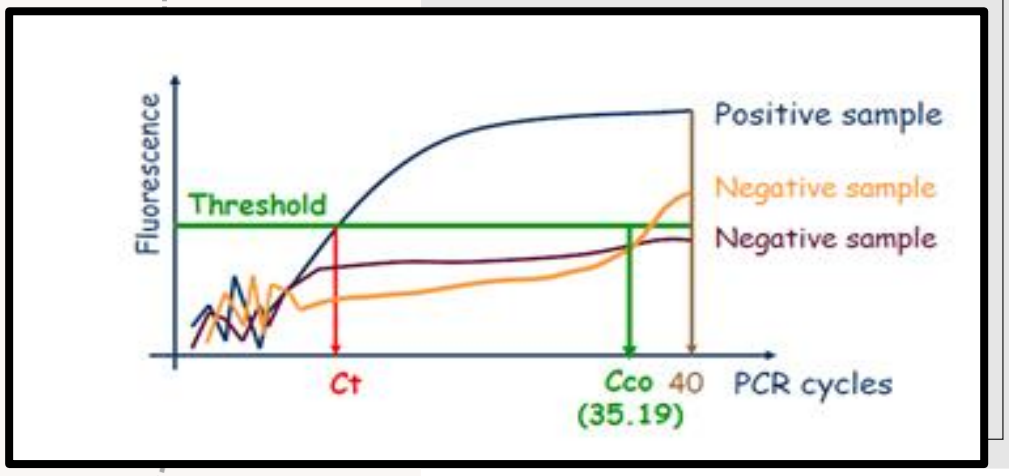
PCR continues to be the backbone of testing for COVID-19







Cycle times (Ct) are the number of times a PCR instrument must cycle through to amplify enough genetic material to be detected



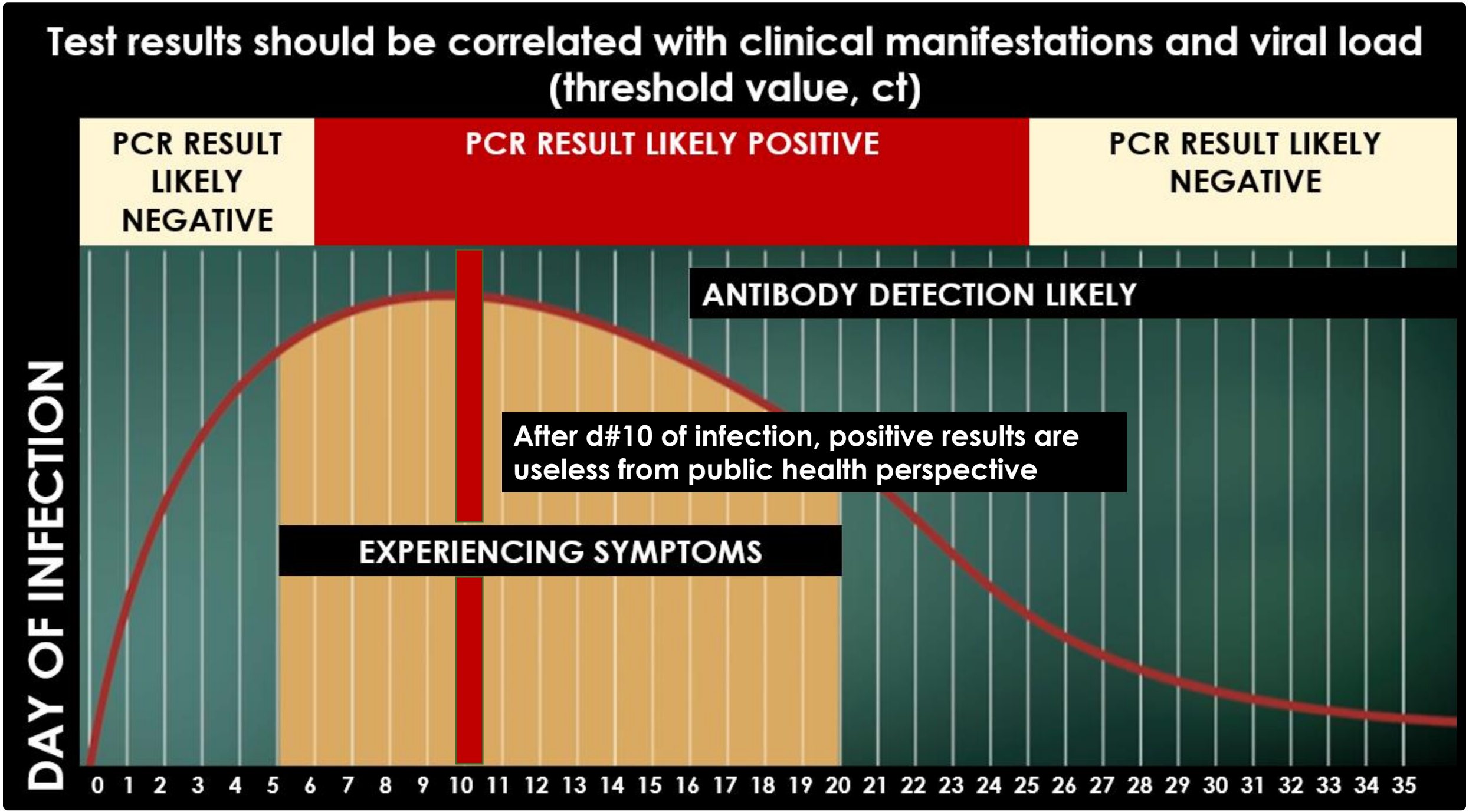
Rapid diagnostic tests: we have 3 general categories (EUA)

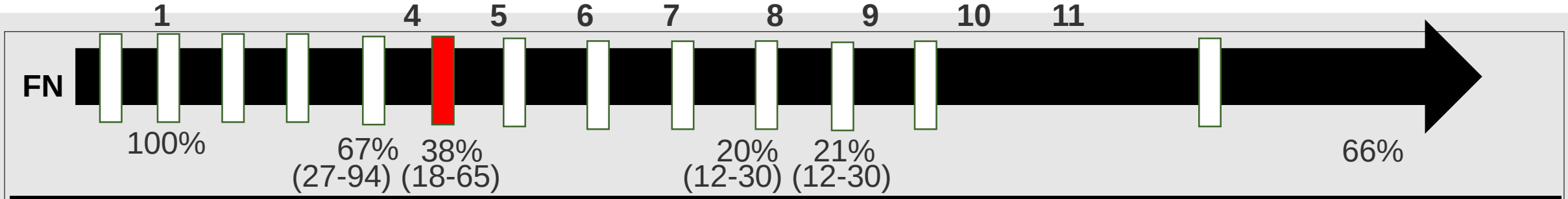
- **RT-PCR (limit of detection= 10-200 copies/mL)**
  - Cepheid[1]: Gold standard: Very accurate
  - Turns around the answer in 45 mins
- **Abbot ID Now[2]=Isothermal NAAT (detects RNA; limit of detection=10k-20k copies/mL) (<13 min)**
  - Sn= 95%; Sp=97.9% (ct < 33 → high titers=infectious)
- **Antigen based test that detects the viral proteins (15 min)**

  1-Quidel[3] Sofia 2= fluorescence immunoassay (FIA) with Lateral flow technology: qualitative detection of nucleocapsid
  - Sn=96.7%; Sp=100% (on par with PCR accuracy)

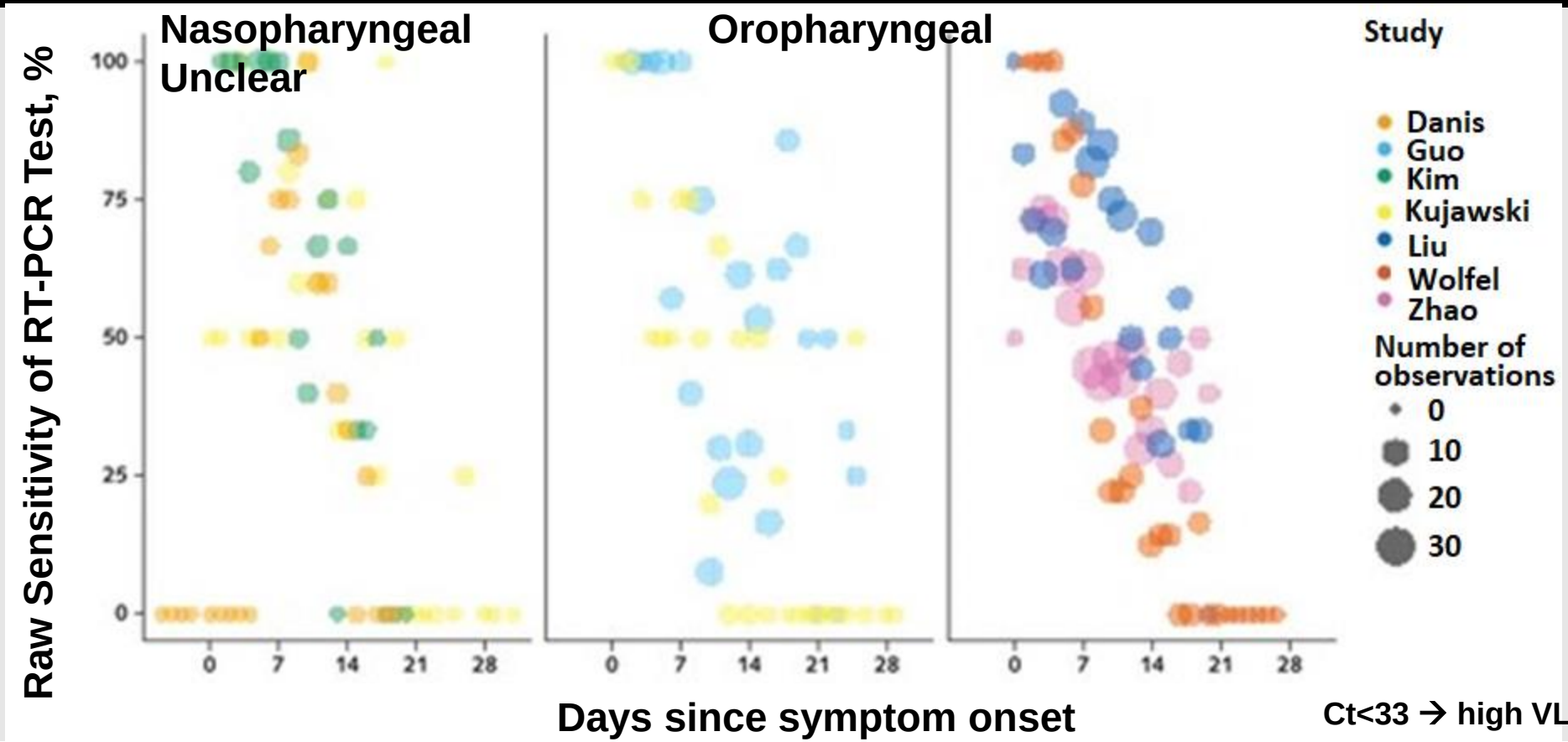
  2-Abbot BinaxNOW[4]: With a swab & a card (15 min) (comes in a card)
  - Sn=97.1%; Sp=98.5%
  - Temporary encrypted digital health pass via QR code (boarding pass)

1-Wolters F, et al. Multi-center evaluation of cepheid xpert® xpress SARS-CoV-2 point-of-care test during the SARS-CoV-2 pandemic. J Clin Virol. 2020; 128: 104426.
2-https://abbott.mediaroom.com/2020-10-07-Abbott-Releases-ID-NOW-TM-COVID-19-Interim-Clinical-Study-Results-from-1-003-People-to-Provide-the-Facts-on-Clinical-Performance-and-to-Support-Public-Health
3-https://www.medtechdive.com/news/quidel-says-its-covid-19-antigen-test-is-now-on-par-with-pcr-accuracy/581902/
4-https://www.abbott.com/corpnewsroom/product-and-innovation/upping-the-ante-on-COVID-19-antigen-testing.html


Test results should be correlated with clinical manifestations and viral load (threshold value, ct)
PCR RESULT LIKELY NEGATIVE
PCR RESULT LIKELY POSITIVE
PCR RESULT LIKELY NEGATIVE
ANTIBODY DETECTION LIKELY
After d#10 of infection, positive results are useless from public health perspective
EXPERIENCING SYMPTOMS
DAY OF INFECTION
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35



Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction–Based SARS-CoV-2 Tests by Time Since Exposure



Ct<33 → high VL

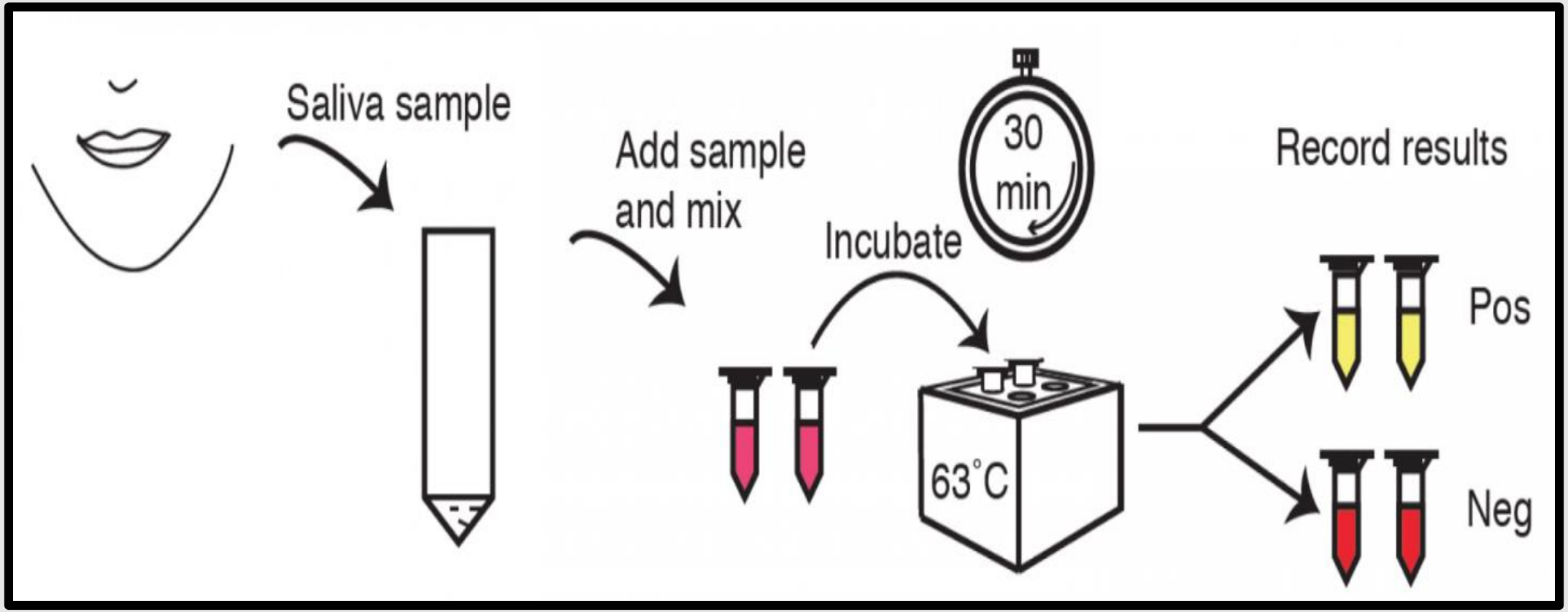
Kucirka L, et al. Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction–Based SARS-CoV-2 Tests by Time Since Exposure. *Ann Intern Med.* 2020; 173(4):262-267.

Can spit solve the COVID-19 problems?

- A meta-analysis of saliva testing studies found 91% (95%CI = 80%-99%) sensitivity for saliva tests and 98% (95%CI 89%-100%) sensitivity for nasopharyngeal swab tests in previously confirmed COVID-19 infected patients, with moderate heterogeneity among studies (using PCR technique)
- Because the genetic materials are unique to COVID-19, the specificity rate is 100%
- Saliva offers a non-invasive specimen that can also be considered for self-sampling.

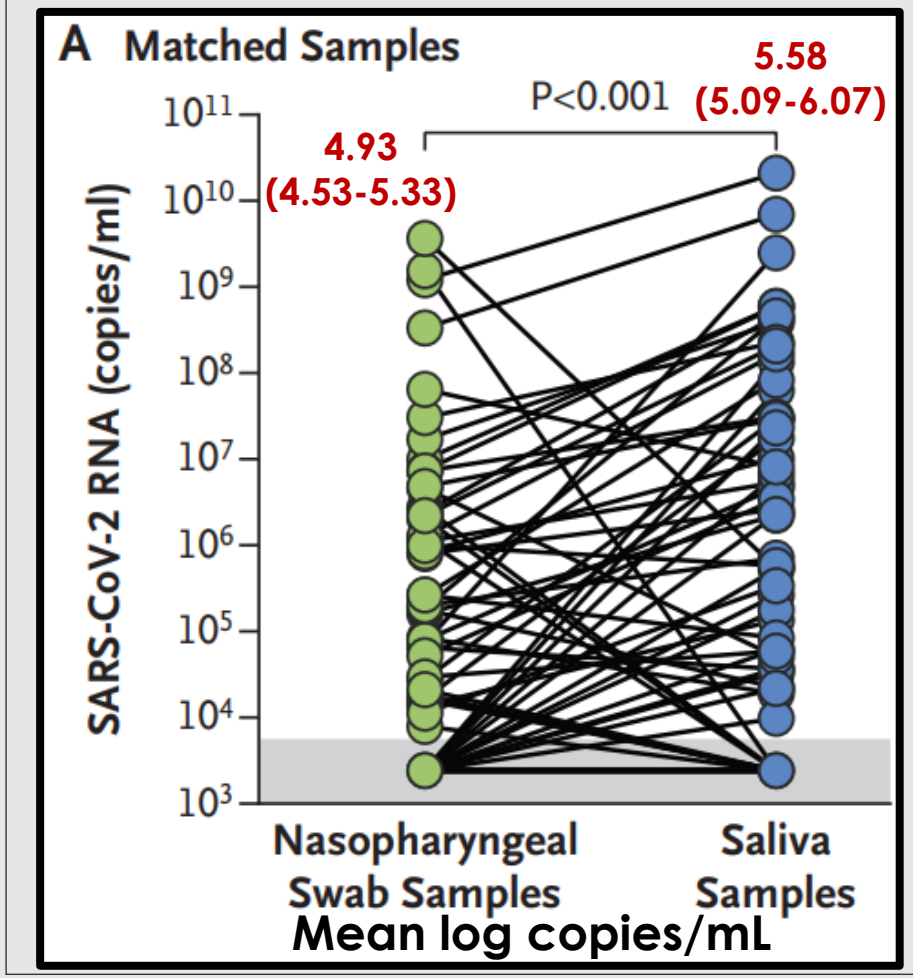
Czumbel LM, Kiss S, Farkas N, Mandel I, Hegyi AE, Nagy AK, et al. Saliva as a Candidate for COVID-19 Diagnostic Testing: A Meta-Analysis. medRxiv. 2020:2020.05.26.20112565.

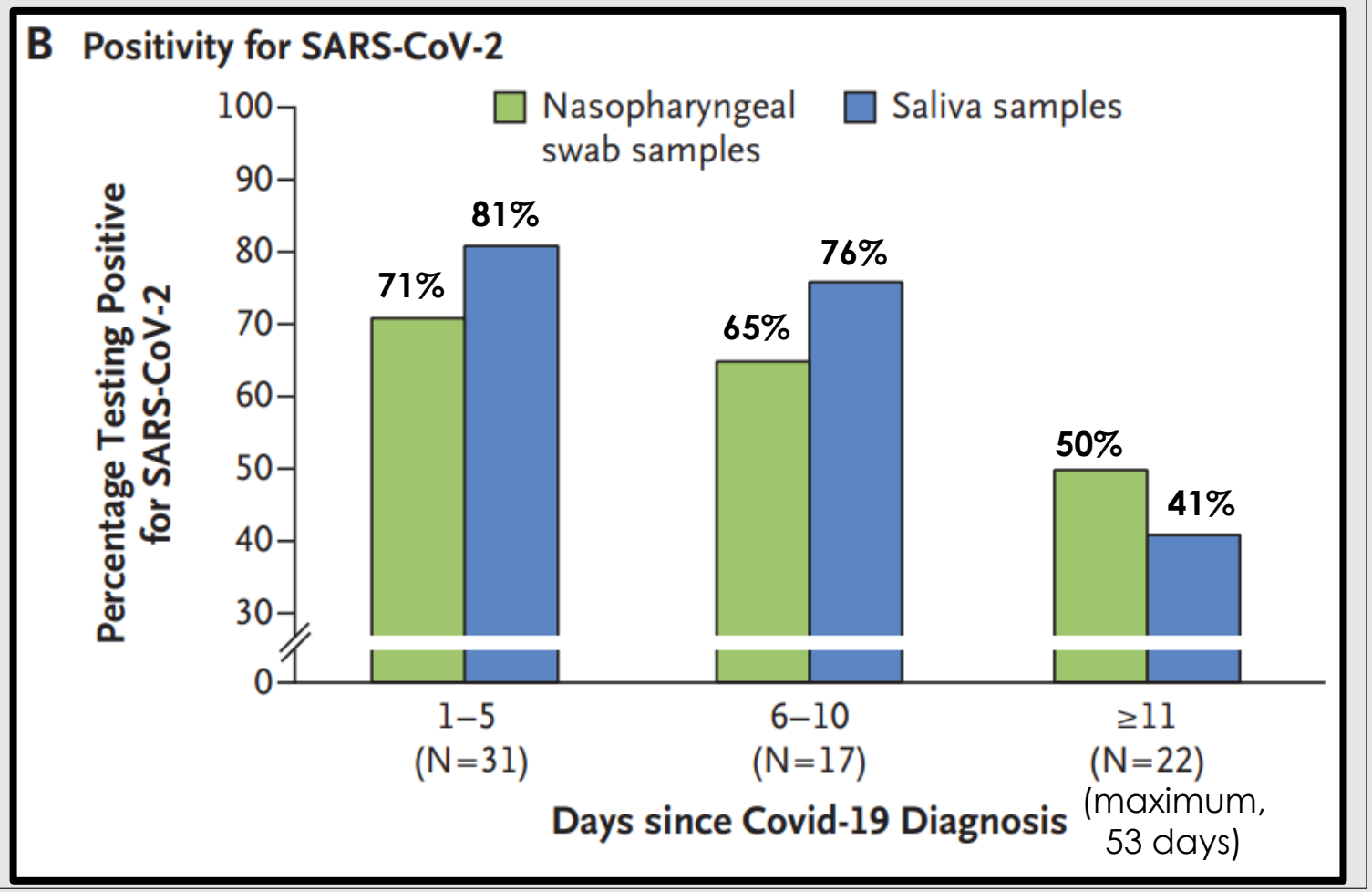
The SalivaDirect test (rapid detection of SARS-CoV-2)



https://www.cuimc.columbia.edu/news/one-two-three-spit-covid-19-test-born-columbia-fertility-clinic

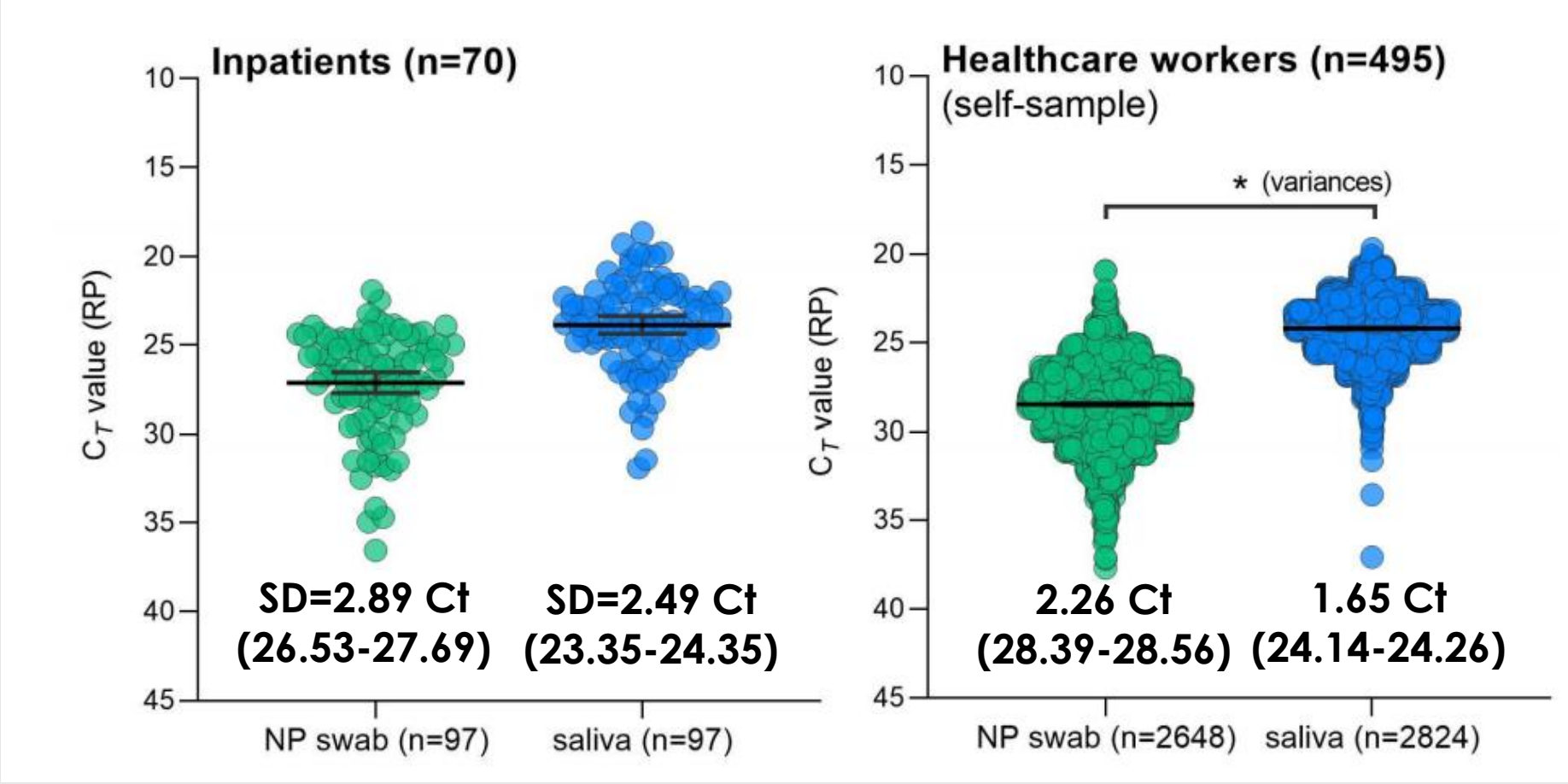
saliva and NP swab specimens for detection of SAR-2 are equal!!!!





Wyllie, AL, et al. Saliva or Nasopharyngeal Swab Specimens for Detection of SARS-CoV-2. N Engl J Med 2020; 383:1283-1286

Greater Variability in NP vs. saliva PCR ct values

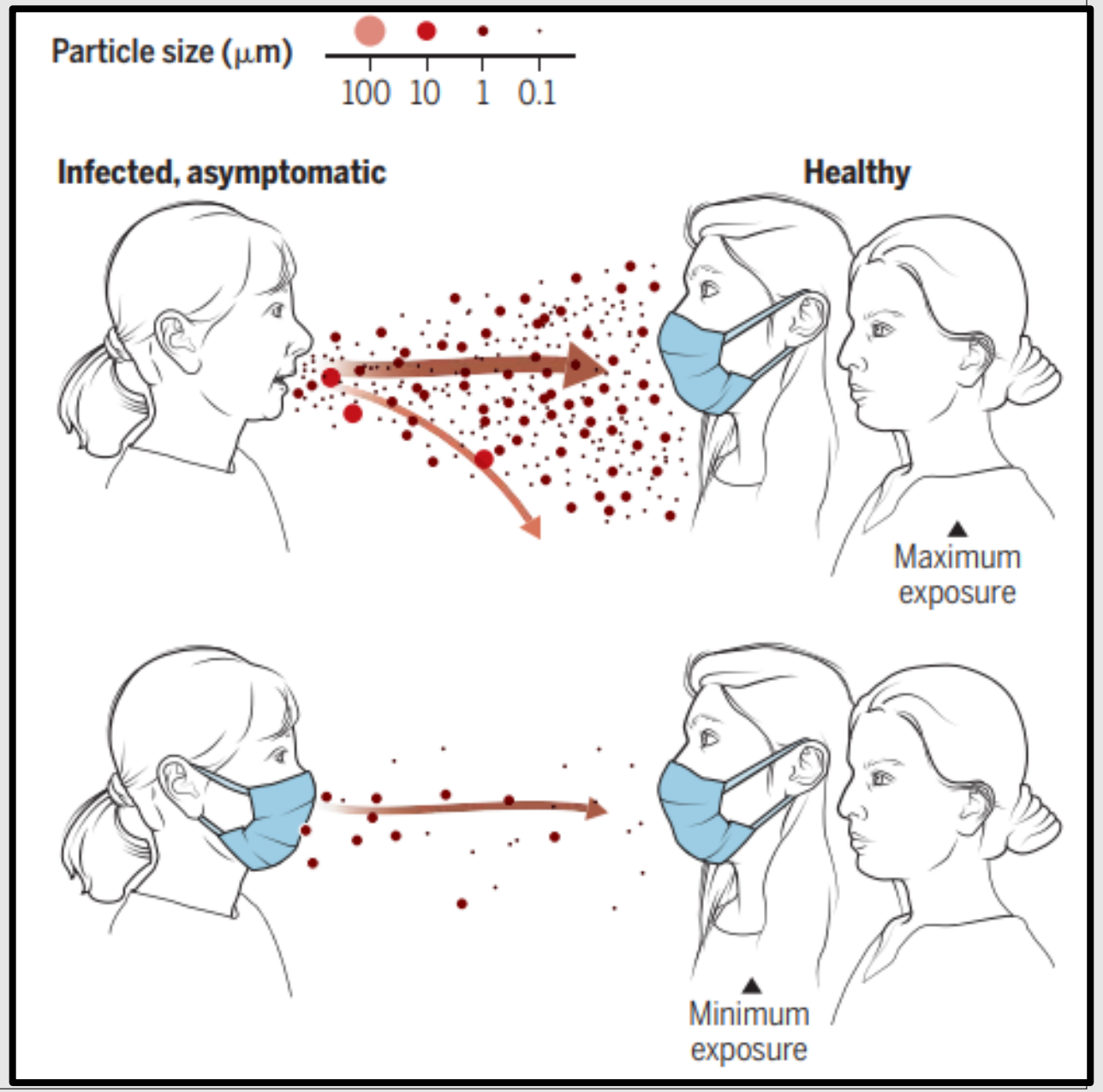


RT-qPCR detection of human RNAse P as a measure of sample quality shows greater variability in the quality of self-collected nasopharyngeal swabs as compared to saliva samples.

Wyllie AL, et al. Saliva or Nasopharyngeal Swab Specimens for Detection of SARS-CoV-2. N Eng J Med. 2020. DOI: 10.1056/NEJMc2016359

Welcome to reality

-**Masks reduce airborne transmission**
-Infectious aerosol particles can be released during breathing and speaking by asymptomatic infected individuals.
-No masking maximizes exposure, whereas universal masking results in the least exposure (best results when all having appropriate and proper face masking).
-**Asymptomatic silent shedders may cause up to 79% of infections.**
-Countries that have reduced spread implemented universal masking (Taiwan, Hong Kong, Singapore, South Korea).



PRATHER KA, ET AL. Reducing transmission of SARS-CoV-2. *SCIENCE*. 2020;368(6498):1422-1424

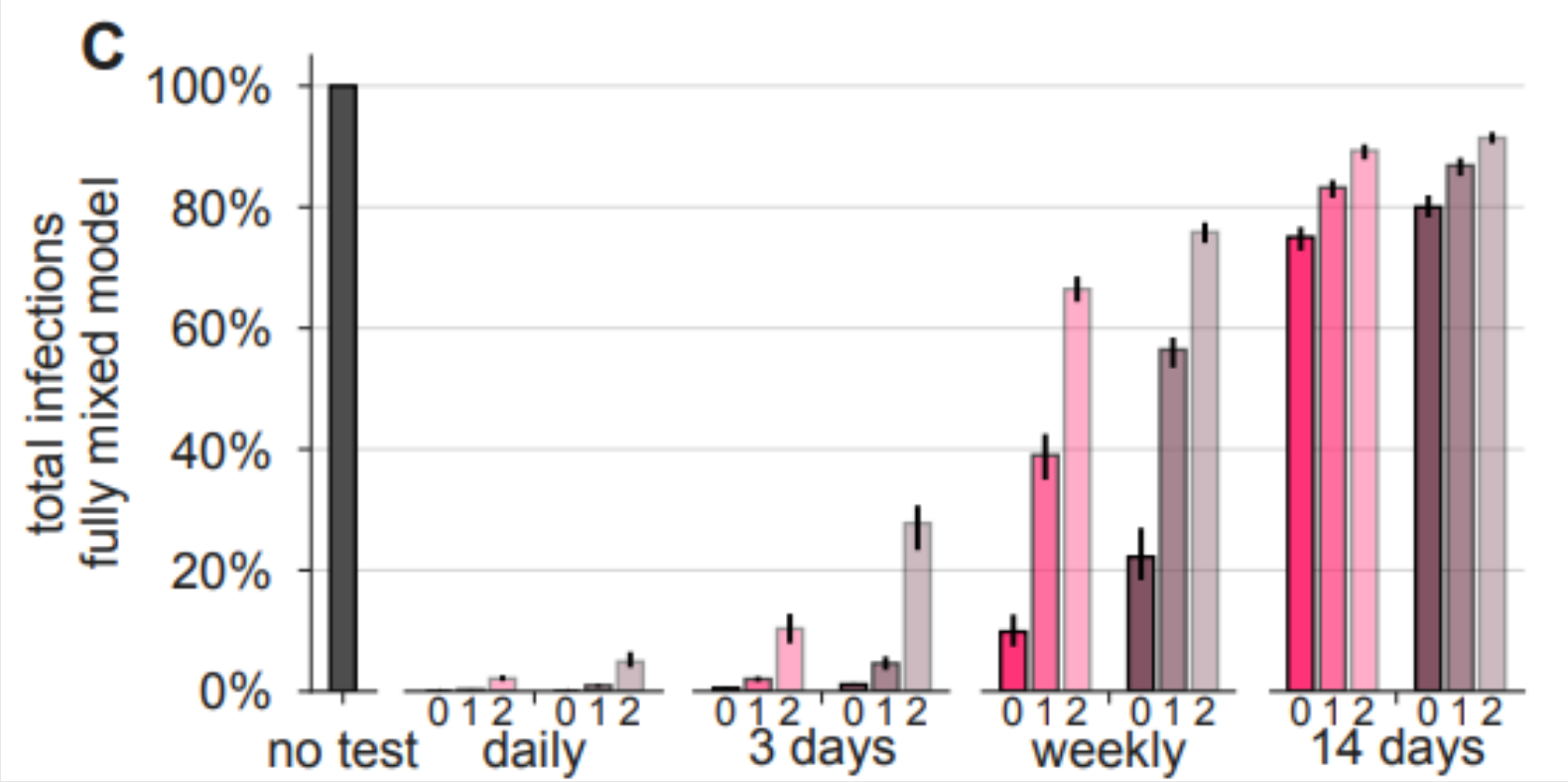
Droplets and airborne routes

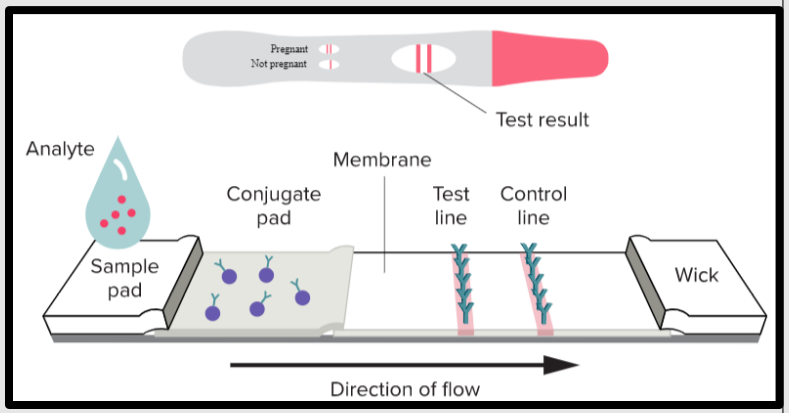
Contact for >15 minutes in proximity <6 feet in the last 24 hours

+

Otherwise you are considered a contact

Time to result + testing frequency are more important than sensitivity to stop outbreaks Virus sensitivity and limit of detection is secondary



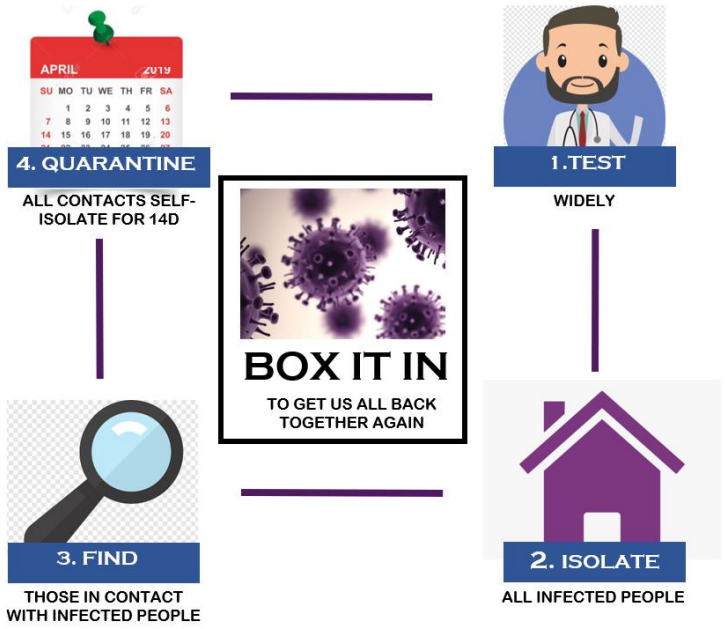


Larremore DB, et .Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance. MedRxiv. 2020. doi: https://doi.org/10.1101/2020.06.22.20136309

Testing

4 corner of the safety box

Mitigation measures



All the paths to sustain life and achieve artificial herd immunity go through
1-widespread testing
2-Ensuring the 4 corners of the safety box
3-Mitigation measures

We need to place this wild virus in cage to regain our freedom