Wisconsin State Laboratory of Hygiene

UNIVERSITY OF WISCONSIN–MADISON

Update on COVID-19 Diagnostic Testing 04-22-20

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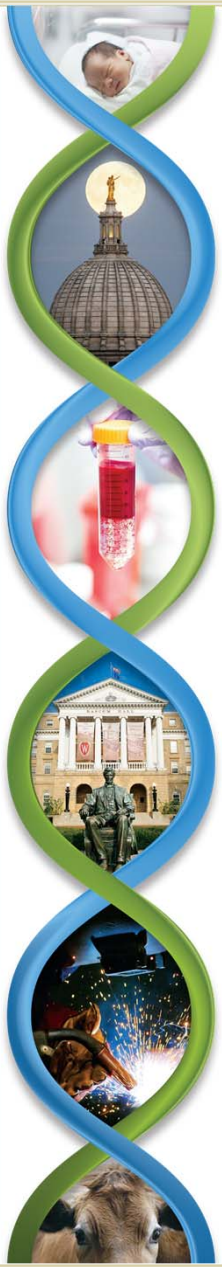


Contents

- Situation Update
- Survey update
- Testing options update
- Data reporting
- Serology
- Q and A

Notice

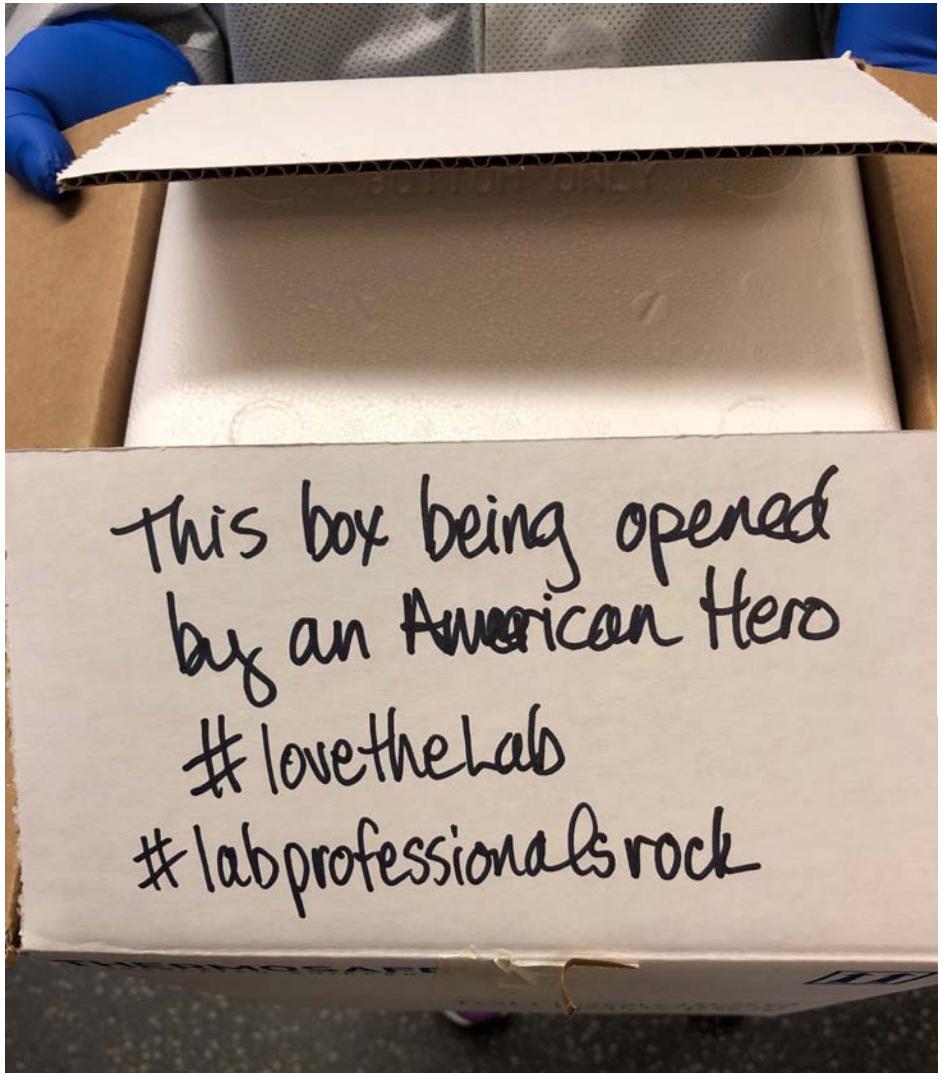
This information is subject to rapid change.

Please refer to our webpage for the most up to date guidance

http://www.slh.wisc.edu/clinical/diseases/covid-19/

The WSLH does not endorse any products

Happy Lab Week!



It's Official!

Governor Evers Proclaims April 19-25

Medical Laboratory Professionals Week!

https://evers.wi.gov/Documents/Proclamations/041920_Proclamation_Medical%20Laboratory%20Professionals%20Week_KO.pdf

STATE *of* WISCONSIN

OFFICE *of the* GOVERNOR

Proclamation

WHEREAS, laboratory testing is crucial to ensuring accurate disease detection, diagnosis, and treatment that physicians and patients depend on to help answer important questions about an individual's health, from cholesterol levels to genetic disorders to cancer detection; and

WHEREAS, medical laboratory professionals uncover health issues by testing and carefully analyzing blood, body fluids, and tissue samples; and

WHEREAS, laboratory scientists and technicians that belong to this profession put their skills and training to use in a variety of settings, from hospitals to physicians' offices to private clinical laboratories, and are important members of medical teams across Wisconsin, meeting the health care needs of Wisconsinites 24 hours a day, seven days a week; and

WHEREAS, this Medical Laboratory Professionals Awareness Week, the State of Wisconsin joins individuals and organizations across our state in celebrating the efforts of Wisconsin's medical laboratory professionals and highlighting the important role they play in ensuring the health and well-being of our state's residents:

NOW, THEREFORE, I, Tony Evers, Governor of the State of Wisconsin, do hereby proclaim the week of April 19 – 25, 2020, as

MEDICAL LABORATORY PROFESSIONALS WEEK

throughout the State of Wisconsin and I commend this observance to all of our state's residents.

IN TESTIMONY WHEREOF, I have hereunto set my hand and caused the Great Seal of the State of Wisconsin to be affixed. Done at the Capitol in the city of Madison this 30th day of March 2020.

Tony Evers

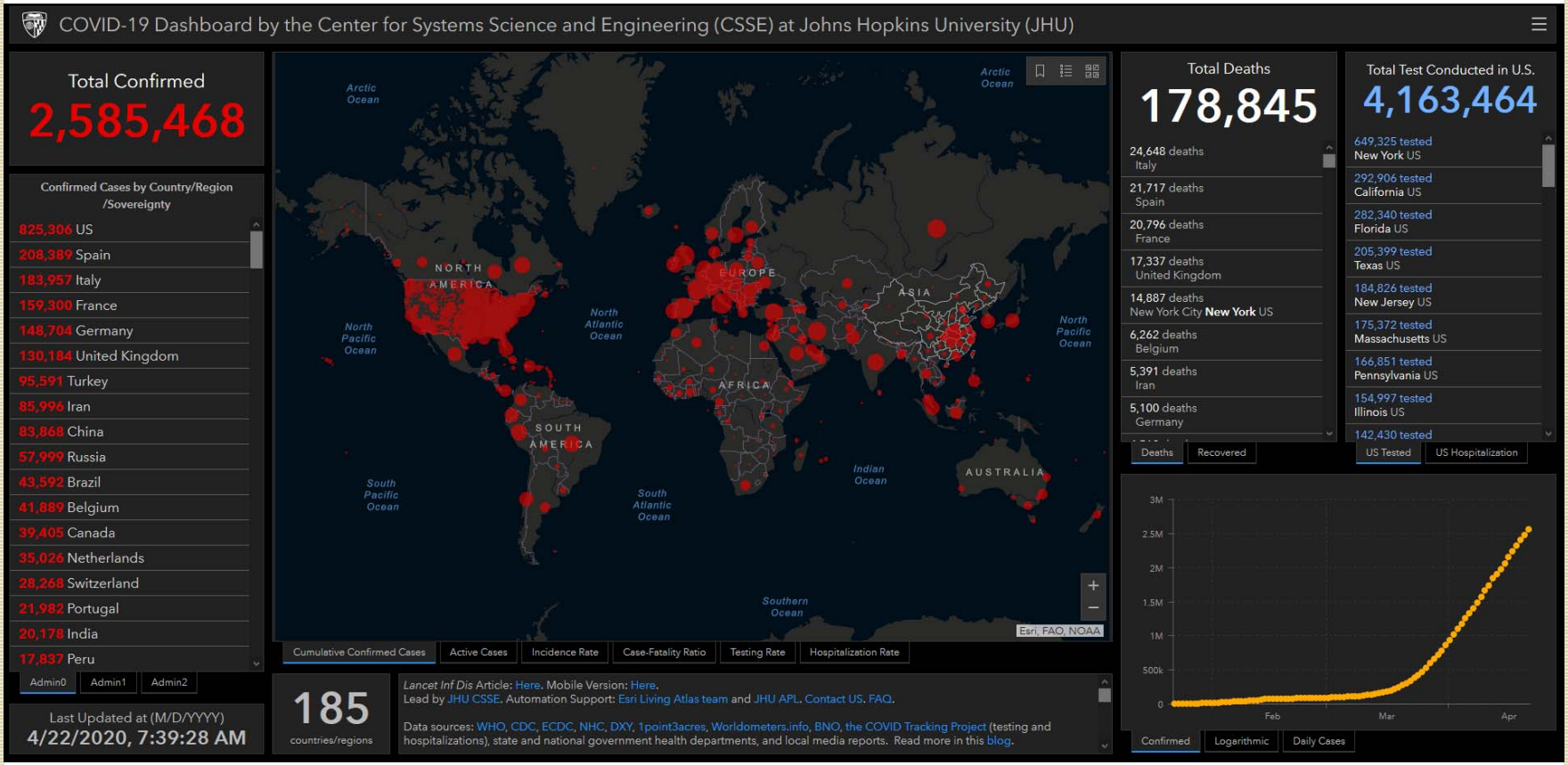
TONY EVERS
GOVERNOR

By the Governor:

Douglas La Follette

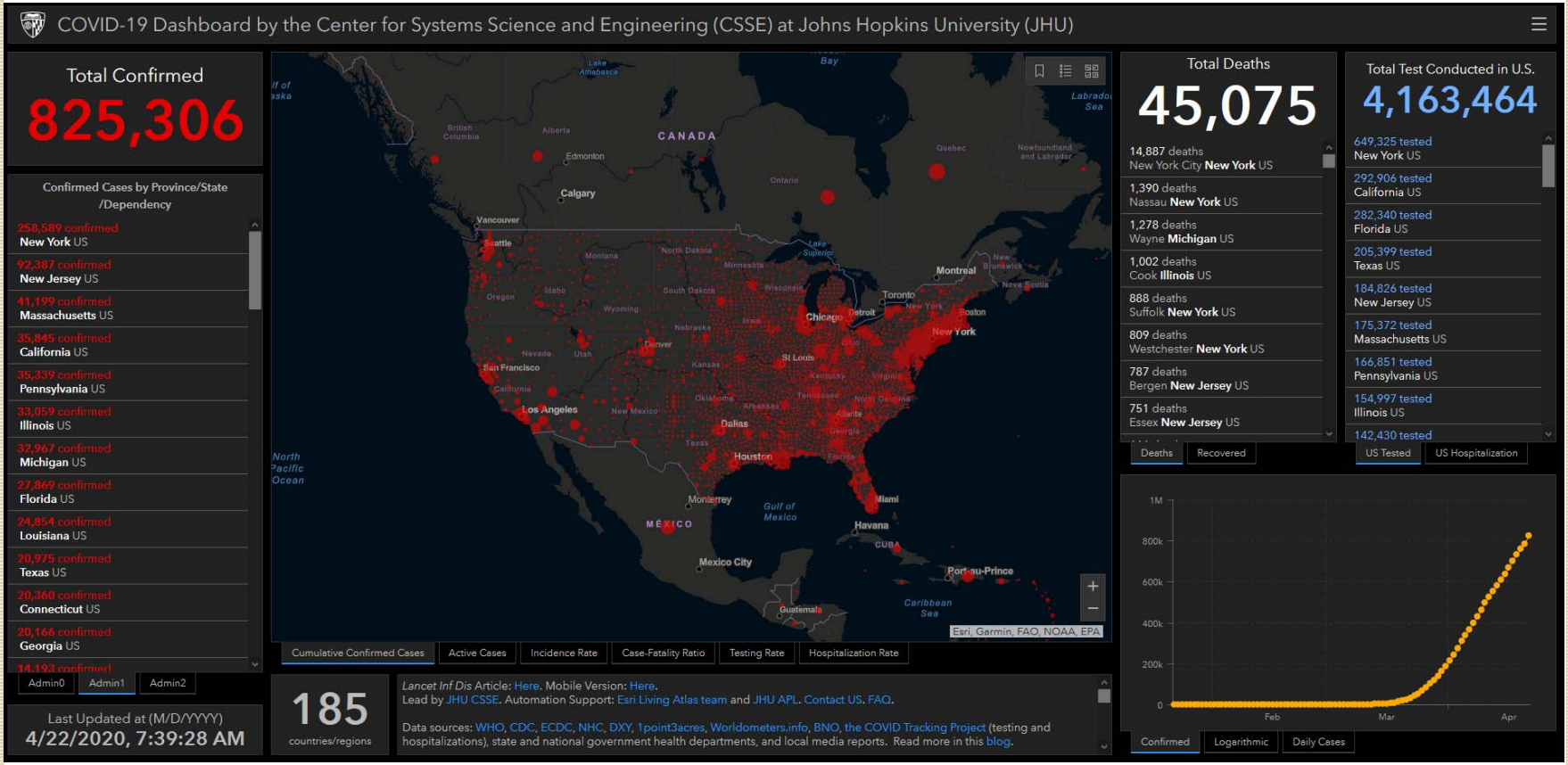
DOUGLAS LA FOLLETTE
Secretary of State

Global Impact

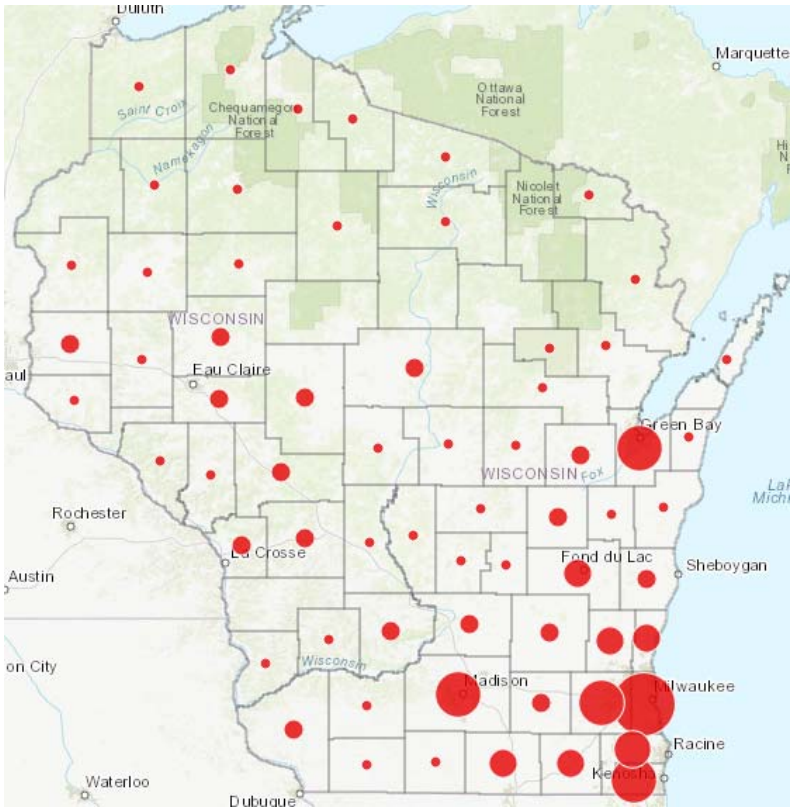


Johns Hopkins University Global Coronavirus Tracking:
https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6

COVID-19 in the US

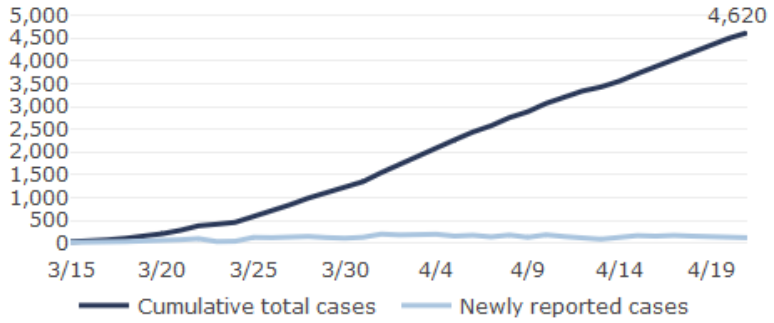


Wisconsin



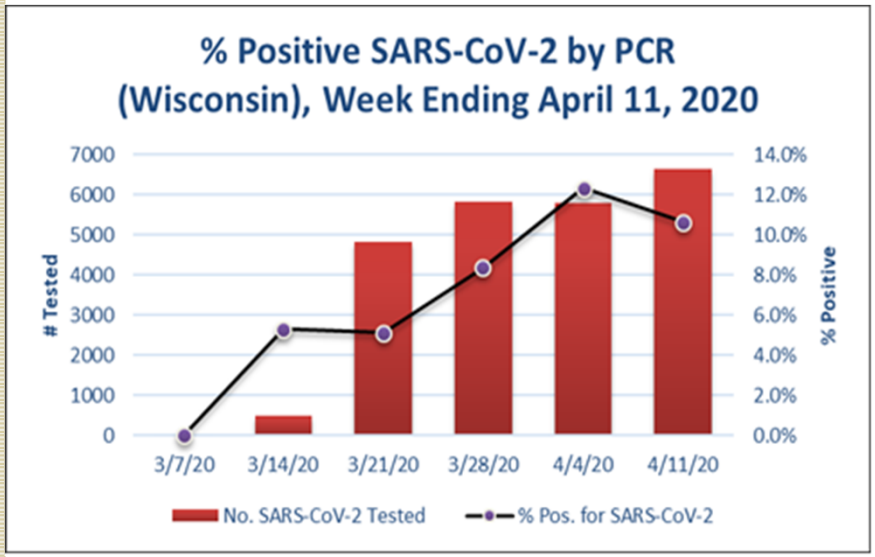
Status	Number (%) of People as of 4/21/2020
Negative Test Results	47,841
Positive Test Results	4,620
Hospitalizations	1,252 (27%)
Deaths	242

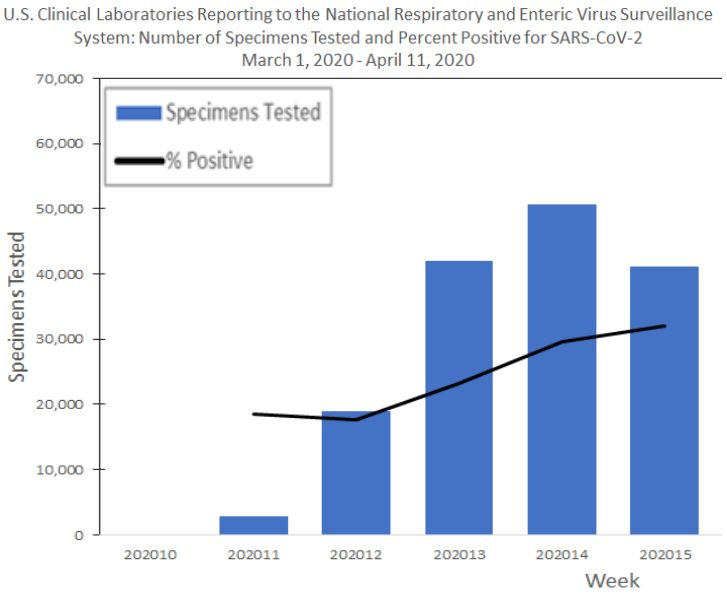
Updated: 4/21/2020



https://www.dhs.wisconsin.gov/outbreaks/index.htm

COVID-19 Testing





http://www.surveygizmo.com/s3/389222/Wisconsin-Laboratory-Surveillance-Reporting

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

*Not all labs reporting

Reminder to Update the Survey

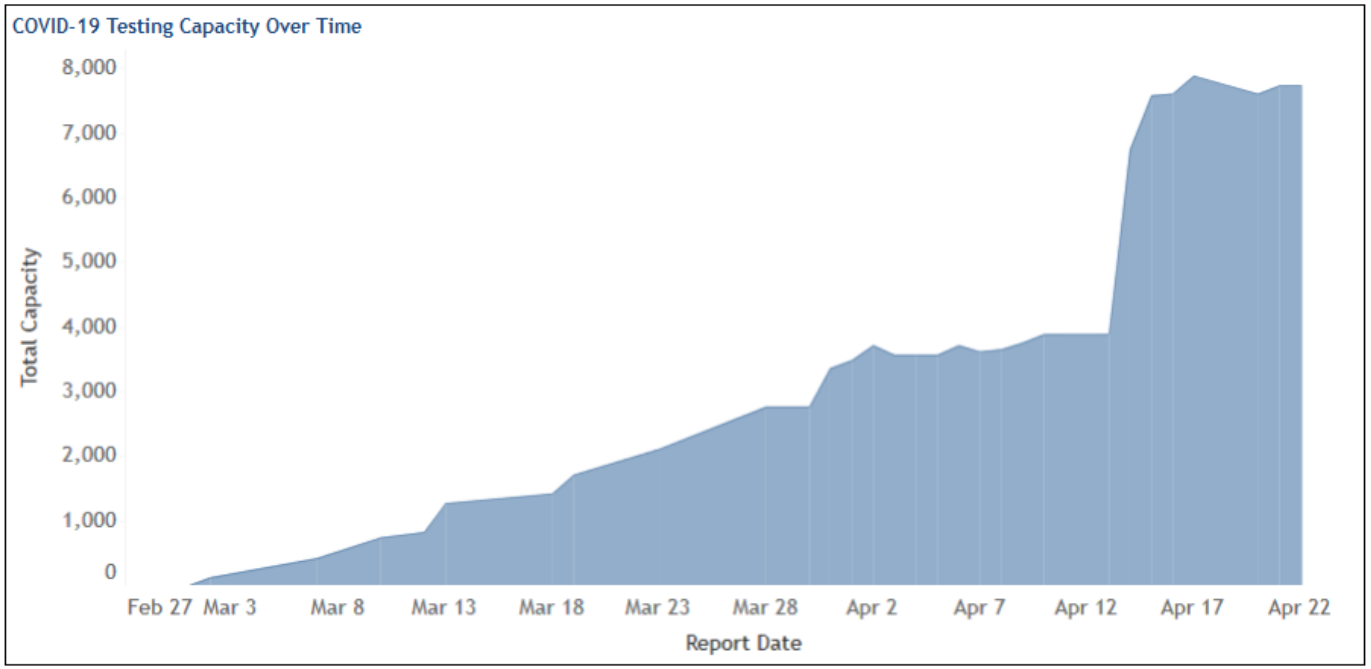
- First time to check for accuracy
- Update when there is a change in testing
  - Start testing for the first time
  - Add or change testing methods
  - Increase or decrease in testing capacity
  - Report major reagent/supply limitations
    - Collection kits
    - Testing components
  - Remove a shortage report

https://covidlabsurvey.wi.gov

Survey Results

Wisconsin COVID-19 Laboratory Testing Capacity

Laboratories actively testing	Laboratories planning to test	Current state capacity (tests/day)
49	35	7,901



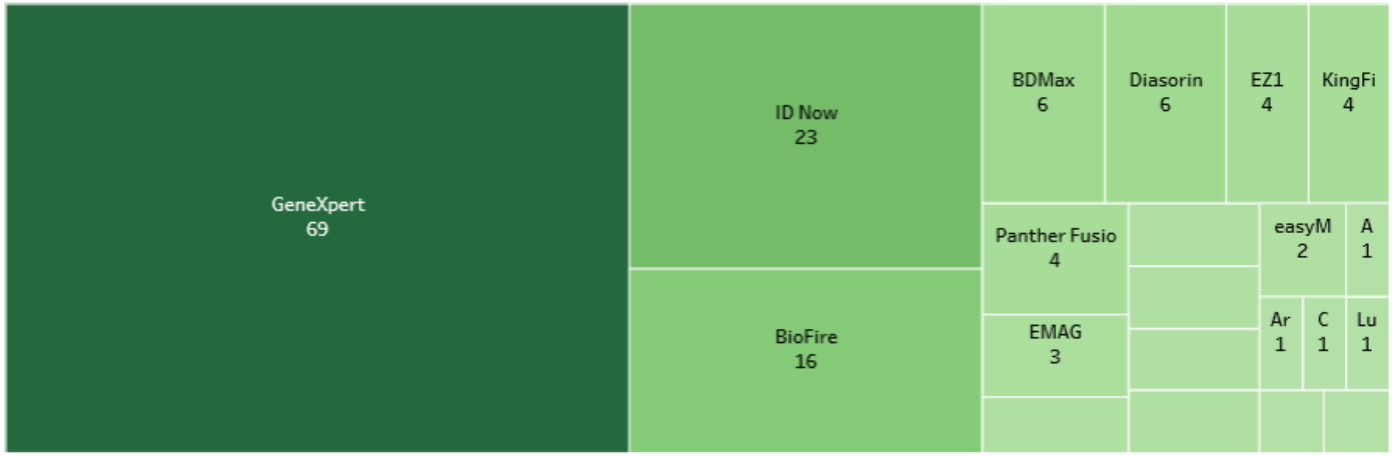
Data collected by voluntary reporting from public, private, and commercial laboratories in Wisconsin. All data are estimates and do not reflect actual number of tests performed in the state. Capacity is dependent on availability of test supplies and adequate staffing

https://bi.wisconsin.gov/t/COVID19_Analytics/views/LabDashboards/PublicDashboard?:origin=card_share_link&:embed=y&:isGuestRedirectFromVizportal=y

What Tests are Being Used?

Active Test Methods Statewide

Current and Planned Methods



https://bi.wisconsin.gov/t/COVID19_Analytics/views/LabDashboards/TestingMethods?:origin=card_share_link&:embed=y&:isGuestRedirectFromVizportal=y

What are the Challenges?

# of reports	Problems
43	GeneXpert cartridges
19	Collections Kits (NP swab and/or VTM)
13	Abbott ID Now cartridges
5	BioFire supplies
3	EMAG/EasyMAG supplies
3	BD Max supplies
2	Abbott ID Now Instruments
1	PPE

*Please continue to submit these updates!

How has your data helped?

- State Distribution Center created to provide collection kits and swabs
- Informed on state guidance to clinicians to broaden testing
- Letters from the Governor sent to Cepheid, BioFire, ThermoFisher, and BioMerieux
- Used by labs to predict which reagents are in highest demand and when new tests hit Wisconsin.

Emergency Supplies

- Quantities limited, available on allocation
- Intended to allow continuity of testing
- Available at no charge

Collection supplies available

- Locally produced VTM kits with NP swabs
- M4 Remel VTM kits with NP swab (limited)
- Exact Sciences kits (Nasal swab with saline)
- NP swabs alone (limited)

Call the WSLH Clinical Orders Department

1-800-862-1088

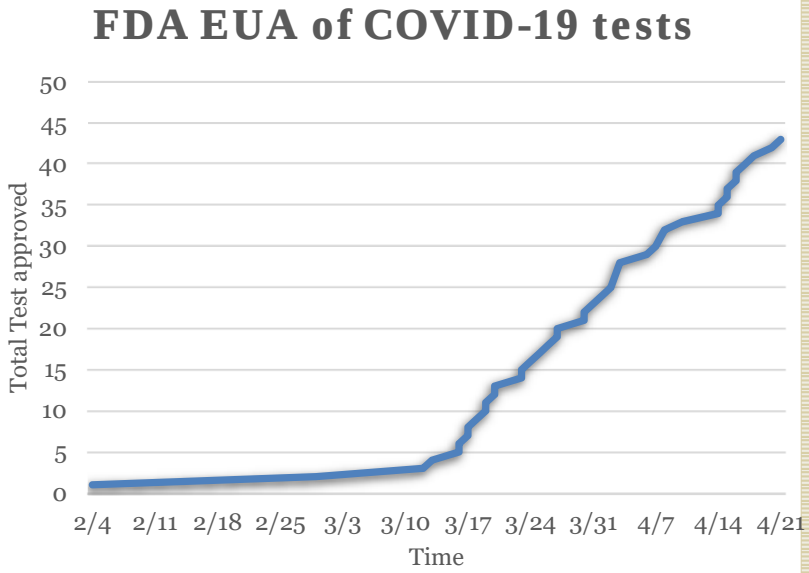
Mon-Fri 7:45 AM – 2:45 PM

Online ordering to come!

New FDA EUA Assays

6 new assays are all primer/probe kits with separate extraction

- SARS-CoV-2 Fluorescent PCR Kit (Maccura Biotechnology (USA) LLC)
- GS™ COVID-19 RT-PCR KIT (GenoSensor, LLC)
- Fosun COVID-19 RT-PCR Detection Kit (Fosun Pharma USA Inc.)
- GeneFinder COVID-19 Plus RealAmp Kit (OSANG Healthcare)
- PhoenixDx 2019-CoV (Trax Management Services Inc.)
- Allplex 2019-nCoV Assay (Seegene, Inc.)



FDA notified (Non-EUA) assays

Manufacturers that have notified FDA that they have validated and are offering serology tests as set forth in Section IV.D:

Where the Authorization Status is "FDA Authorized," the FDA reviewed and issued an EUA for the test after notification was given. Where the Authorization Status is shown as "Not FDA Authorized," the FDA has not yet reviewed the manufacturer's validation and issued an EUA for the manufacturer's test, and the test is included in this list to provide transparency regarding the notifications submitted to FDA. The "Setting for Use" designation of "H" refers to a laboratory certified under CLIA to perform high-complexity testing.

Search:

Manufacturer and Test	Authorization Status	Settings for Use[2]
Abbott Laboratories SARS-CoV-2 IgG (for use on ARCHITECT)	Not FDA Authorized	H
Alfa Scientific Designs, Inc. Clarity COVID-19 IgG/IgM Antibody Test	Not FDA Authorized	H
Alfa Scientific Designs, Inc. Instant-view plus COVID-19 IgG/IgM Antibody Test	Not FDA Authorized	H
Anhui Deepblue Medical Technology Co., Ltd. COVID-19 (SARS-CoV-2) IgG/IgM Antibody Test Kit (Colloidal Gold)	Not FDA Authorized	H
Artron BioResearch Inc./ Artron Laboratories Inc. Artron COVID-19 IgM/IgG Antibody Test	Not FDA Authorized	H
Assure Tech (Hangzhou) Co., Ltd.'s COVID-19 IgG/IgM Rapid Test Device	Not FDA Authorized	H
Atlas Link (Beijing)Technology Co., Ltd NovaTest: One Step COVID-19 IgG/IgM rapid test	Not FDA Authorized	H

https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-diagnostic-testing-sars-cov-2

Home Self Collection

LabCorp “Pixel” self collection at home avoids the healthcare system and preserves PPE

Requires Physician order

https://www.pixel.labcorp.com/blog/introducing-self-collection-kits-covid-19-testing

Abbott ID NOW COVID-19 Assay

- Recent study by Cleveland Clinic showed false-negative rate of 14.8% using ID NOW.
- Abbott responded that problems with the test could stem from samples being stored in VTM before being tested instead of being inserted directly into the ID Now testing machine.
- Abbott statement – "When a direct swab is used, the test is performing as expected"

https://www.npr.org/sections/health-shots/2020/04/21/838794281/study-raises-questions-about-false-negatives-from-quick-covid-19-test

Reporting COVID-19 Results

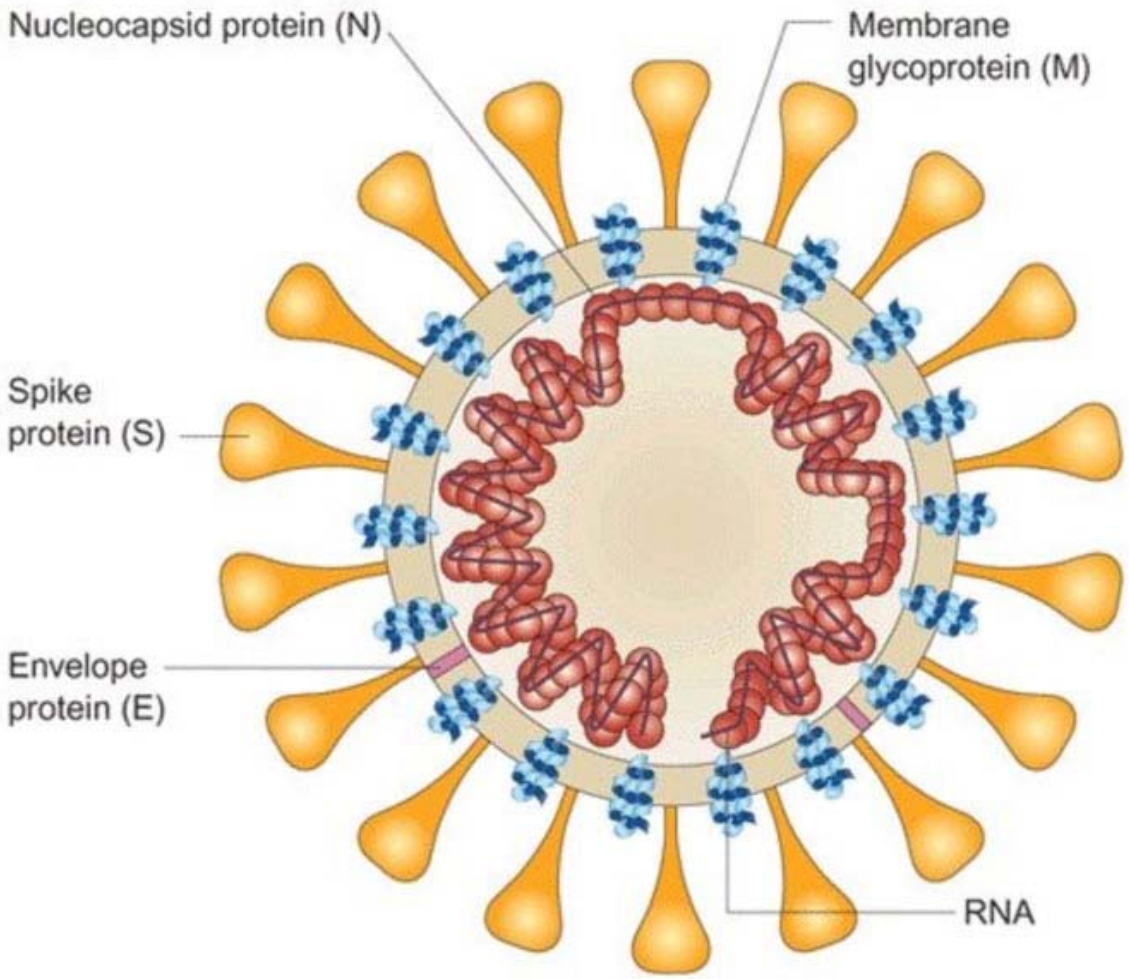
- Report **all** COVID-19 test results in WEDSS via ELR or WLR
  - COVID-19 testing performed in-house
  - COVID-19 testing sent to a reference lab
- Report weekly total number of positives and total number tested to WCLN Surveillance Data
  - COVID-19 testing performed in-house
  - COVID-19 testing performed at out-of-state reference lab
- Report daily to HHS per VP Pence letter

CDC COVID-19 Updated Healthcare Safety Information

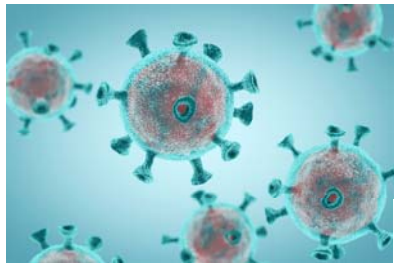
- ***Updated*** **Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed COVID-19 in Healthcare Settings** – This guidance has been updated to include the recommendation that all U.S. healthcare facilities put policies into place requiring everyone entering the facility to practice source control, regardless of symptoms.
- Healthcare personnel (HCP) should wear a facemask at all times while they are in a healthcare facility.
- This recommendation does not change CDC's guidance for healthcare personnel to use N95 or equivalent respirators when providing care for patients with suspected or known COVID-19.

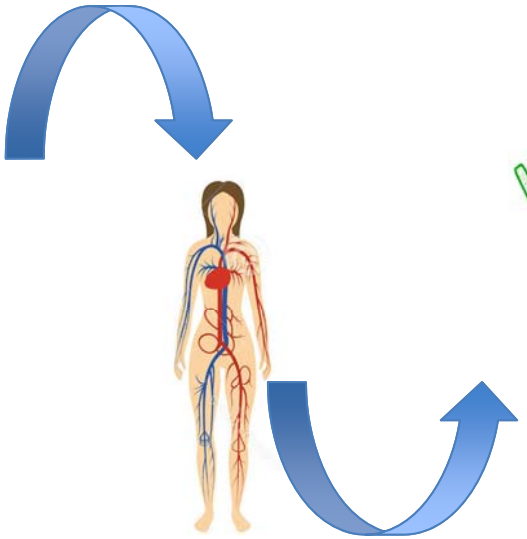
Serology

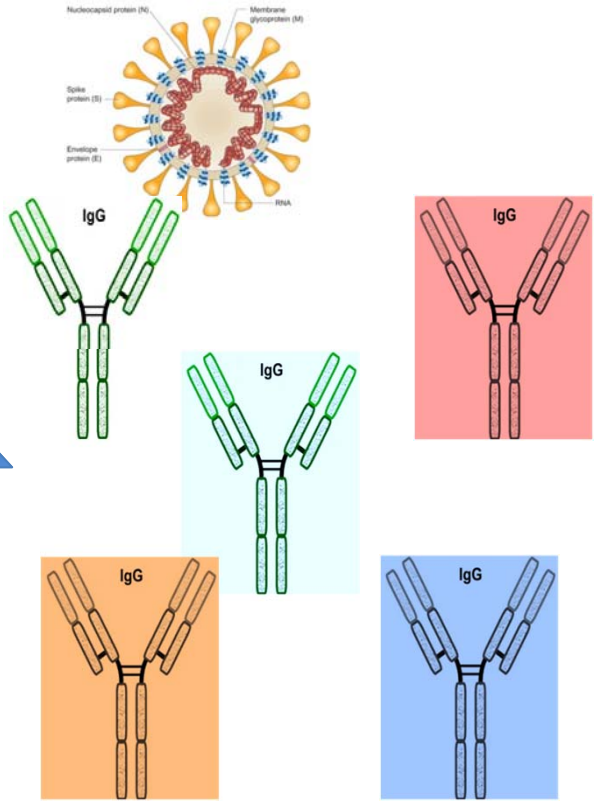
Coronavirus

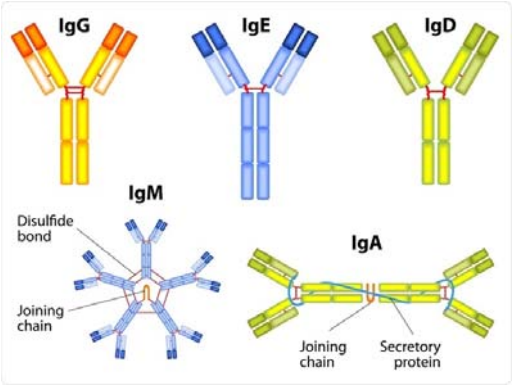


Quick Immunology Review



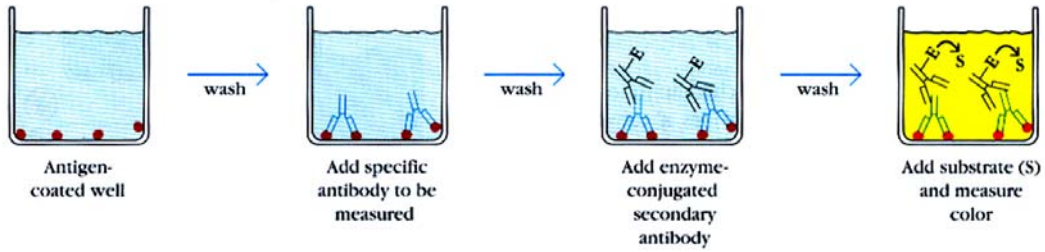






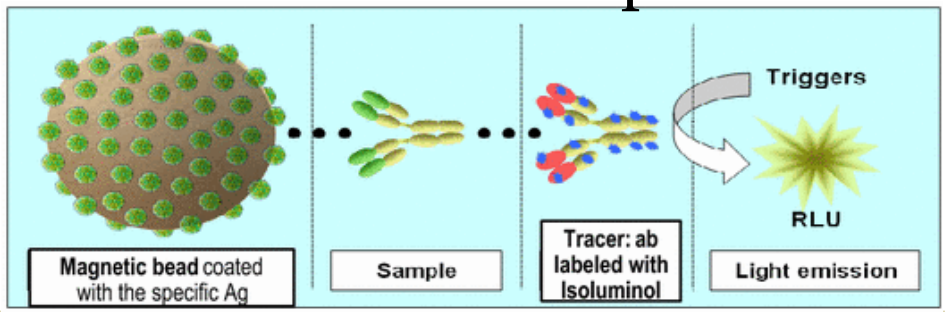
How do the Different Tests Work?

ELISA (Enzyme Linked ImmunoSorbent Assay)

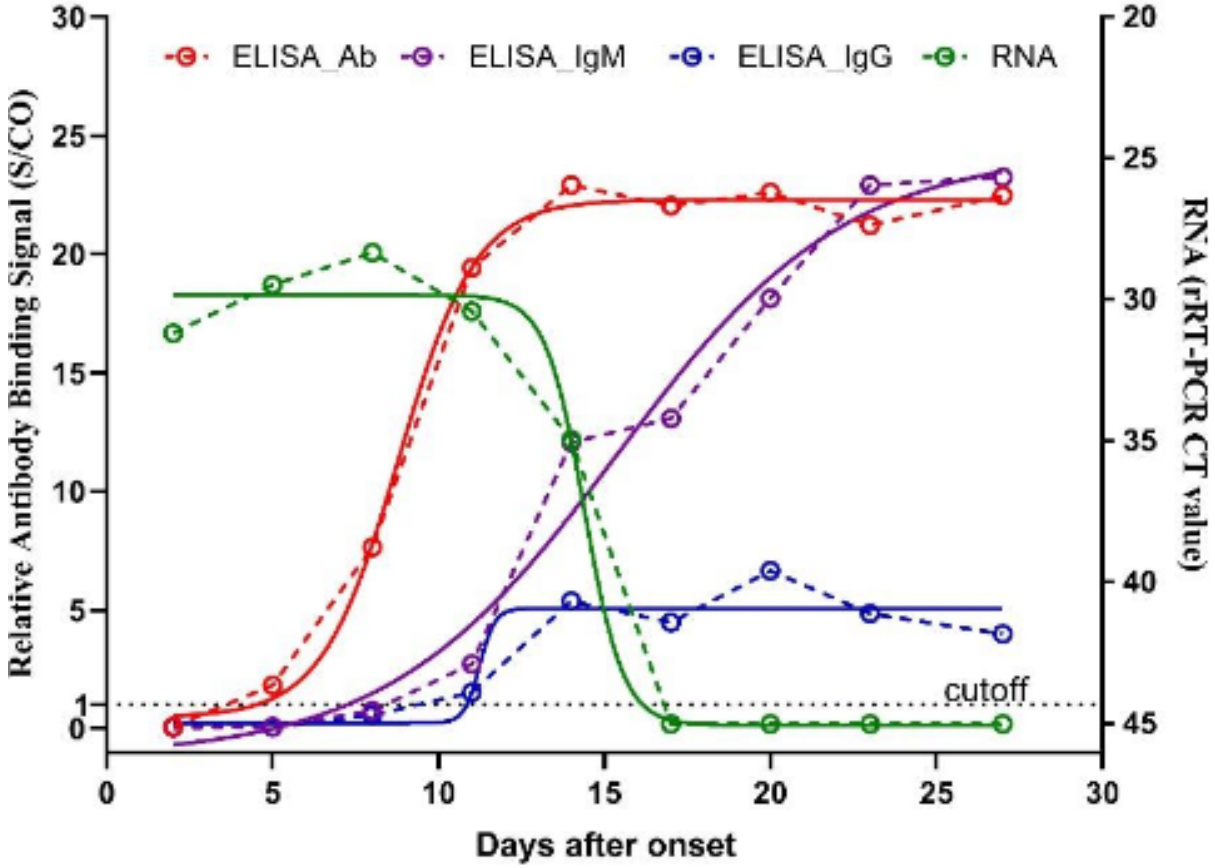


Lateral Flow Assays

CMIA (Chemiluminescent microparticle immunoassay)



Time Frame for Detection



https://www.medrxiv.org/content/10.1101/2020.03.23.20041707v1.full.pdf

Sero-prevalence of seasonal Cov

18-24% of Children

HCoVs	Positive			Negative		
	All	IgG+ (%)	IgG– (%)	All	IgG+ (%)	IgG– (%)
NL63	21	5[a](23.8)[b]	16 (76.2)	246	142 (57.7)	104 (42.3)
229E	30	7 (23.3)	23 (76.7)	246	124 (50.4)	122 (49.6)
OC43	38	7 (18.4)	31 (81.6)	246	123 (50.0)	123 (50.0)
HKU1	26	6 (23.1)	20 (76.9)	246	133 (54.1)	113 (45.9)

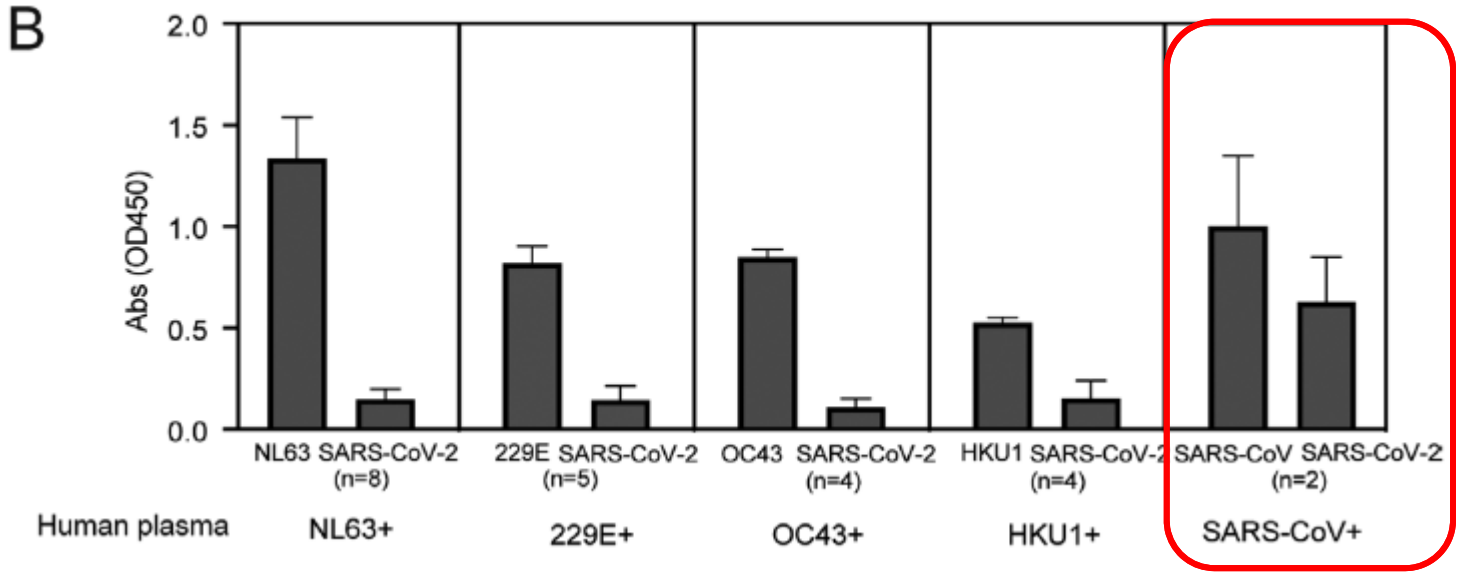
https://www.sciencedirect.com/science/article/pii/S01634531500225X#fig1

91-100% of Adults >50

Strain	No. of positive samples (%)/ total no. of samples tested	GMT of all sera[a]	IgG antibody to HCoV in serum: Only sera with detectable antibody		
			GMT	Median	Range
Group I					
HCoV-229E	104 (99)/105[c]	994[d]	1,022	1,038	127–23,706
HCoV-NL63	103 (98)/105[c]	567[d,e]	595	629	109–3,095
Group II					
HCoV-OC43	105 (100)/105[c]	1,235[d,e]	1,235	1,137	127–45,816
HCoV-HKU1	96 (91)/105[c]	466[d,e]	575	527	106–8,392

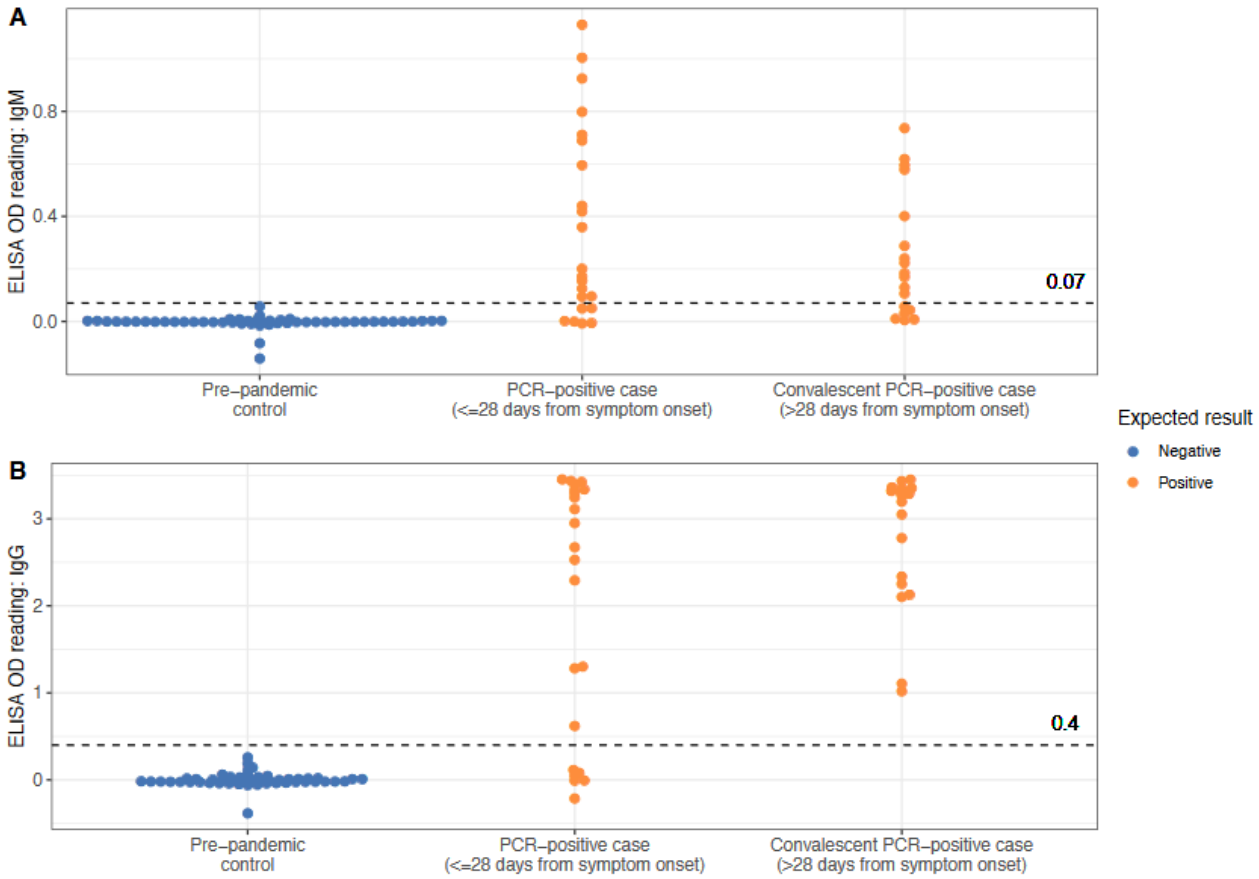
https://cvi.asm.org/content/cdli/17/12/1875.full.pdf

Cross reactivity with other coronaviruses



https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa310/5810754

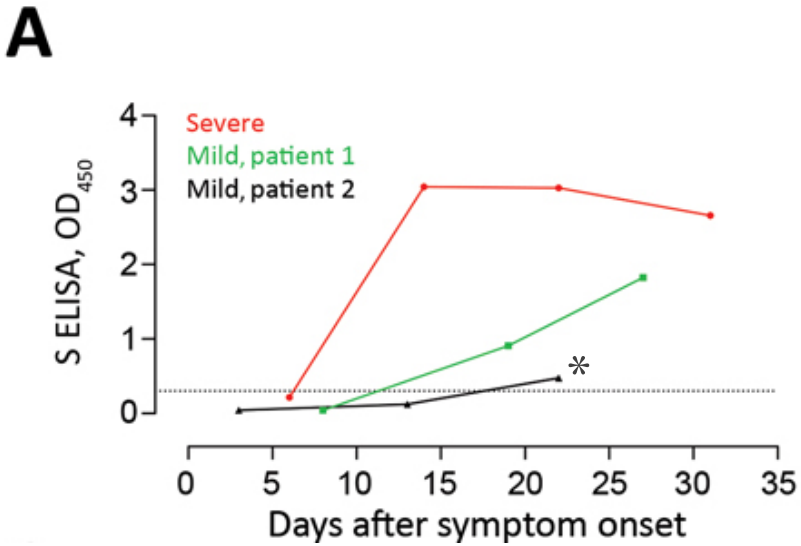
Minimal Cross Reactivity with seasonal CoV



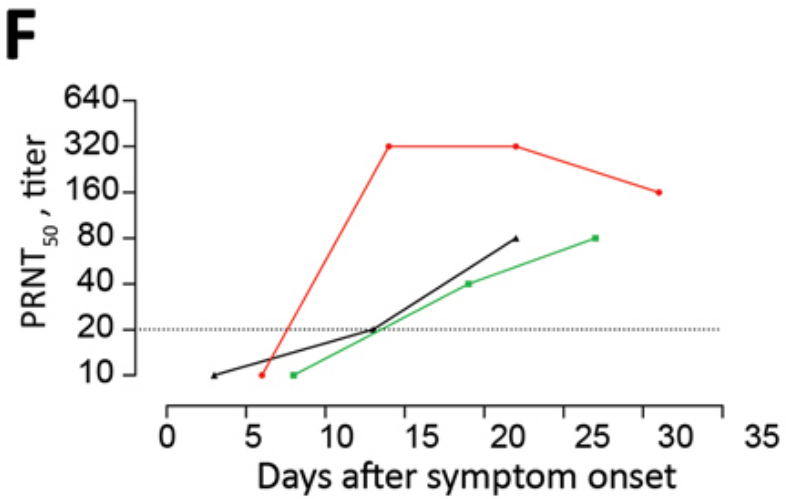
https://www.medrxiv.org/content/10.1101/2020.04.15.20066407v1.full.pdf

Severe disease leads to a more robust immune response

Total S Antibody



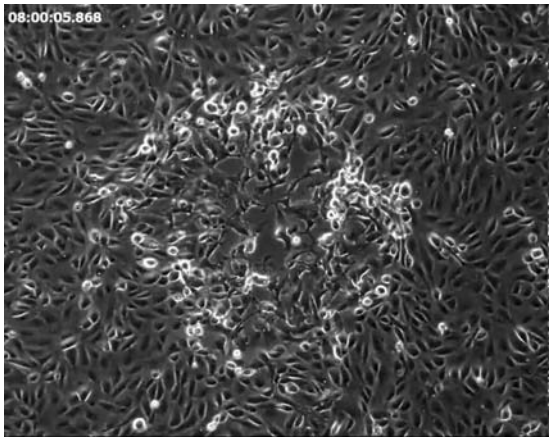
Neutralizing Antibody



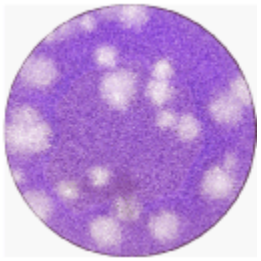
*Some people do not develop detectable antibody responses

https://wwwnc.cdc.gov/eid/article/26/7/20-0841-f1

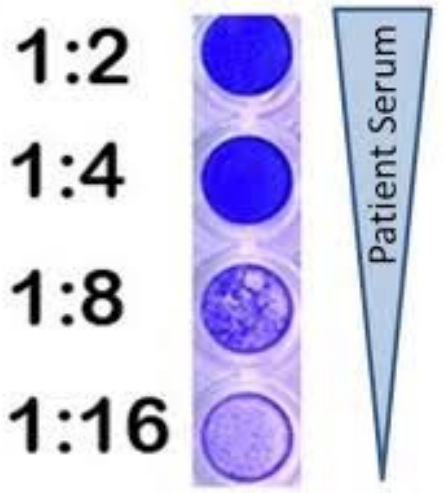
Plaque Reduction Neutralization Test (PRNT)



Uninfected



Infected



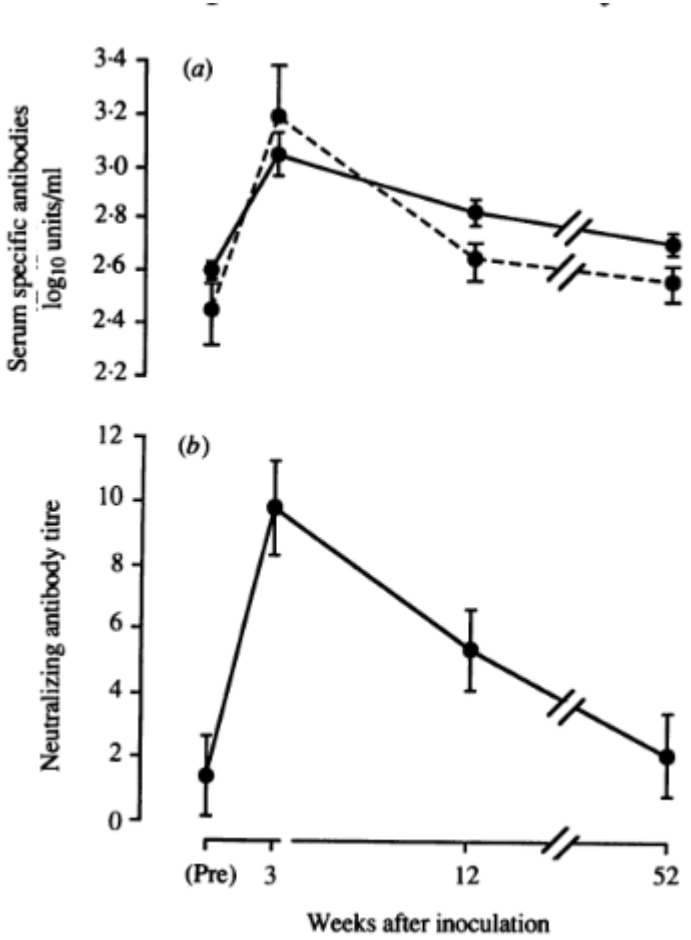
- Time consuming (multiple days)
- Complex (special lab space)
- Subjective (advanced training)
- Biosafety risks (concentrated live virus)

Does Immunity Last?

Neutralizing antibodies to CoV-229E drop after about a year

Subsequent infections tend to be less severe

Could explain seasonality



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2271881/pdf/epidinfect00023-0213.pdf

Re-infection?

- South Korea reporting increasing numbers of cases of re-infection
- About half have symptoms, dead virus?
- Symptoms tend to be mild
- May still be infective, no reports of transmission
- Usually detected within 35 days of “recovery”
- May be due to intermittent shedding or poor collection

https://www.npr.org/sections/coronavirus-live-updates/2020/04/17/836747242/in-south-korea-a-growing-number-of-covid-19-patients-test-positive-after-recover

Re-Cap

- The body develops many kinds of antibodies in response to infection, not all are protective.
- It takes much longer to detect antibodies than virus, making molecular tests better for diagnosis of acute infections.
- Cross reactivity with seasonal Coronaviruses seems to be low. Higher with SARS-1
- Neutralizing antibodies are produced but are hard to test for.
- We don’t know if immunity will last or for how long.

Lateral Flow Assays
Not all created equal

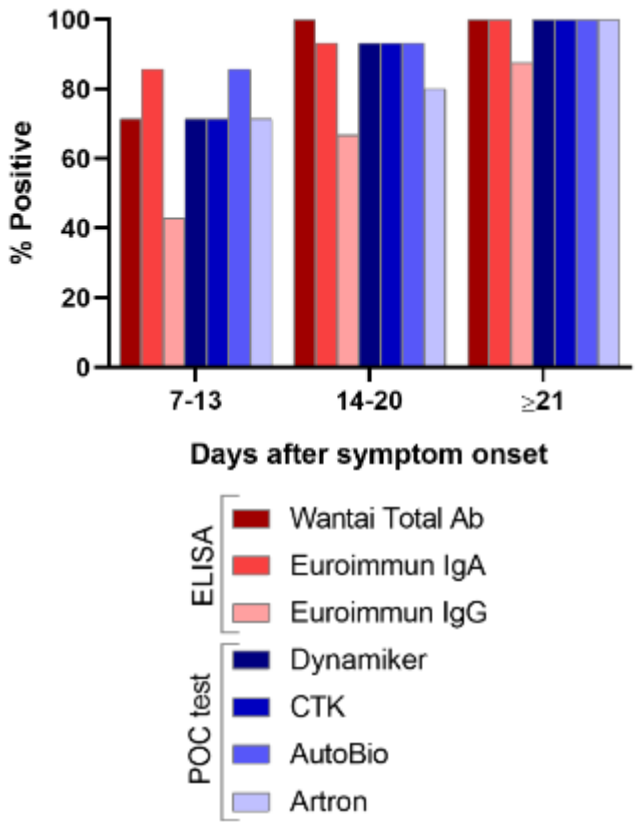
- 9 different lateral flow assays compared to ELISA
- PCR as gold standard
- Specificity high >95%
- Sensitivity low <70%

Assay	RT-PCR positive		Pre-pandemic control		Sensitivity (95% CI)	Specificity (95% CI)
	True positive	False negative	True negative	False positive		
ELISA	34	6	50	0	85 (70,94)	100 (93,100)
1	18	15	60	0	55 (36,72)	100 (94,100)
2	23	15	90	1	61 (43,76)	99 (94,>99)
3	21	12	58	2	64 (45,80)	97 (88,>99)
4	25	13	59	1	66 (49,80)	98 (91,>99)
5	19	12	58	2	61 (42,78)	97 (91,>99)
6	20	11	59	1	65 (45,81)	98 (91,>99)
7	23	10	57	3	70 (51,84)	95 (86,>99)
8	18	14	60	0	56 (38,74)	100 (94,100)
9	22	18	138	4	55 (38,74)	97 (93,>99)

https://www.medrxiv.org/content/10.1101/2020.04.15.20066407v1.full.pdf

Sensitivity Improves Over Time

- 9 different assays
  - 3 ELISA
  - 4 Lateral flow
- PCR as gold standard
- Sensitivity greatest ≥21 days



https://www.medrxiv.org/content/10.1101/2020.04.09.20056325v1.full.pdf

How do the Different Tests Compare?

ELISA

- Time consuming
- Technically challenging

Lateral Flow Assays

- 100+ on the market
- highly variable

CMIA

- Need more data

VITROS® XT Systems

- 150 tests/hour
- Installed in 1000 labs in the US
- Has FDA EUA
  - VITROS Immunodiagnostic Products Anti-SARS-CoV-2 Total Reagent Pack (Ortho Clinical Diagnostics, Inc.)

VITROS Data

Days between PCR positive and Serum Collection*	Number Reactive	Number Non-Reactive	Total Number Tested
1–3	6	2	8
4–6	7	2	9
7–9	2	0	2
Not Provided	15	2	17
Total	30	6	36

* SARS-CoV-2 positive PCR result confirms presence of virus. Immune response in patient is expected to be latent following initial viral infection.

VITROS SARS-CoV-2 Total showed 100% (400/400) negative agreement in 400 presumed SARS-CoV-2 antibody negative subjects and 83.3% (30/36) positive agreement (95% CI: 67.2–93.6%) in 36 PCR positive subjects.

	Comparator method/PCR Positive		
VITROS		Positive	Presumed Negative
	Reactive	30	0
	Non-reactive	6	400

*Their package insert

Abbott Architect i1000 or i2000

- More than 2000 architects in the US
- Mass production of test kits
  - 1 million next week
  - 4 million in April
  - 20 million in June
- 100-200 tests/hour
- They have applied for FDA EUA
- Already shipping tests

Abbott Data

Positive Agreement by Days Post-Symptom Onset

Days Post-Symptom Onset	n	Positive	Negative	PPA (95% CI)
< 3	5	0	5	0.00% (0.00, 52.18)
3 - 7	10	5	5	50.00% (18.71, 81.29)
8 - 13	34	31	3	91.18% (76.32, 98.14)
≥ 14	**73**	**73**	**0**	**100.00% (95.07, 100.00)**

Negative Agreement by Category

Category	n	Positive	Negative	NPA (95% CI)
Pre-COVID-19 Outbreak	997	4	993	99.60% (98.98, 99.89)
Other Respiratory Illness	73	0	73	100.00% (95.07, 100.00)
Total	**1070**	**4**	**1066**	**99.63% (99.05, 99.90)**

*Their package insert

BioRad- EVOLIS

- IgM/IgG/IgA
- Manual or automated on the EVOLIS
- Started Shipping yesterday
- They have applied for FDA EUA
- Reporting “99 Percent Specificity and 98 Percent Sensitivity”

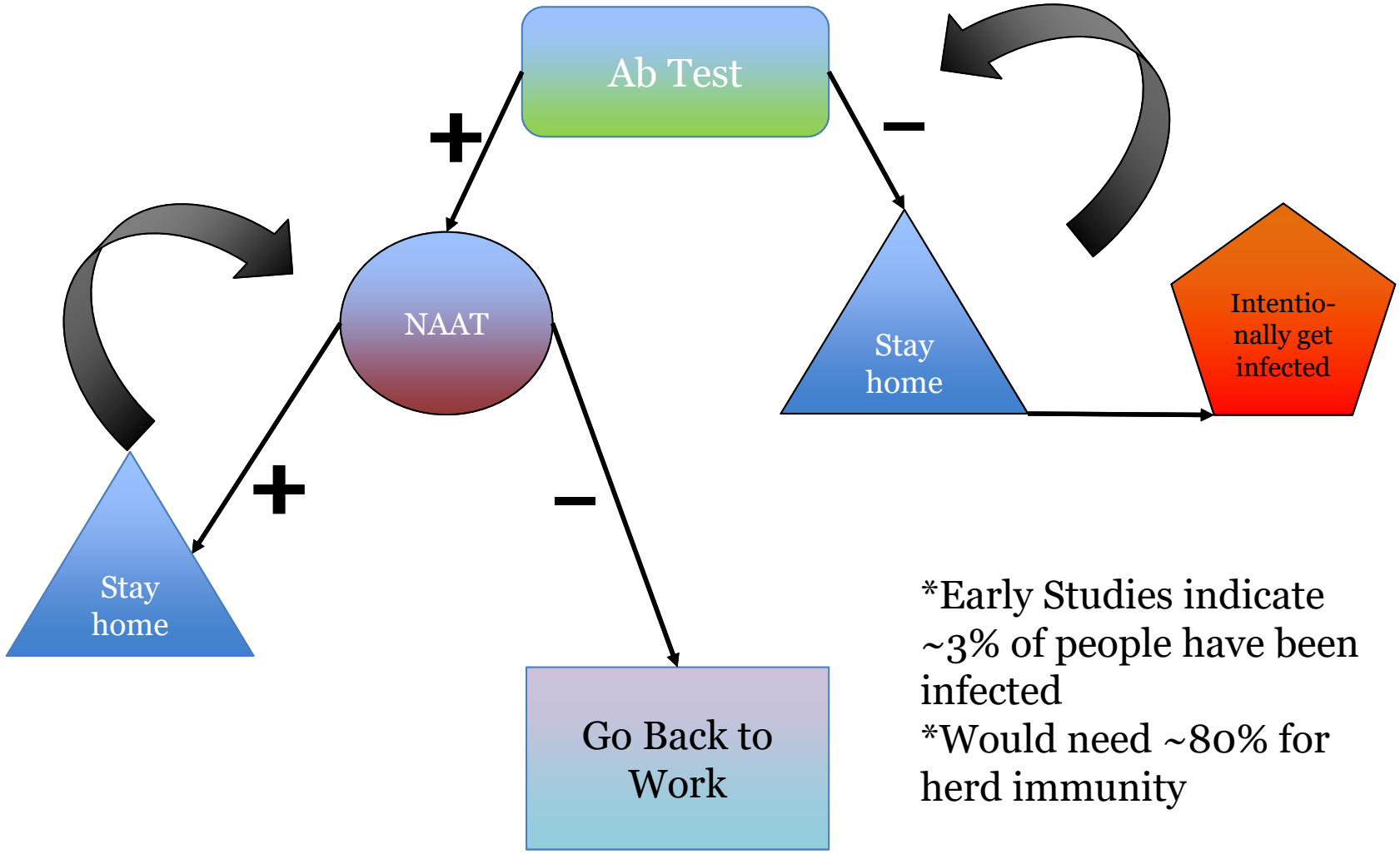
DiaSorin- LIAISON

- They have applied for FDA EUA
- IgG antibodies directed against the S1 and S2 domains
- Up to 170 patient sera samples per hour
- About 500 platforms in the US

Siemens - Centaur

- Seeking FDA EUA
- 240 tests/hour

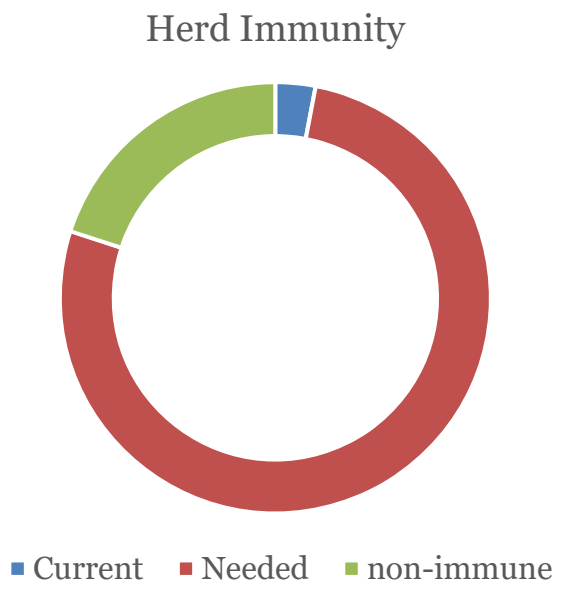
Option 1- Return to work testing



*Early Studies indicate ~3% of people have been infected
*Would need ~80% for herd immunity

Option 2- Ab Surveillance

- Track Prevalence to inform policy
  - If rate higher than NAAT suggests virus may be less dangerous than we thought
- Test until we reach herd immunity status
  - Current surveys ~3% are positive
  - ~80% of the population would need to be immune for herd immunity (based on infectivity)



*Vaccine still a long way off

https://www.sciencemag.org/news/2020/04/antibody-surveys-suggesting-vast-undercount-coronavirus-infections-may-be-unreliable

Option 3- the Swedish approach

Open wide to let immunity develop naturally

- At current 5% death rate= 232,880 dead*
- If we are missing 2/3 of cases so death rate is actually only 1.7%= 79,179 dead*

*Assuming transmission stops when ~80% have been infected
**Based on Wisconsin population of 5.822 M

Option 4- Massive NAAT

- Test everyone that wants it
- Follow-up with every positive for case investigation and quarantine to stop transmission chains

Badger Bounce Back Plan

- Estimates 85,000 tests per week needed
  - Current capacity 55,307/week (supply dependent)
- 1000+ Epidemiologists

- Current stay at home orders gave us time to develop testing to make this possible.

A clear use for Serology

Testing previous positive patients prior to donation for Plasma therapy of COVID-19 infection

- Neutralizing antibodies
- Shown to help severely ill patients

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

Serology

- Antibodies take multiple days longer to detect a positive than NAAT.
- These tests cannot be used to diagnose a patient.
- Testing for return to work has problems
- They could be used for sero-prevalence
- Massive NAAT with case investigation more likely to be a solution
- Testing prior to plasma donation is useful

Additional Resources

FDA Serology Guidance for clinicians

https://www.fda.gov/medical-devices/letters-health-care-providers/important-information-use-serological-antibody-tests-covid-19-letter-health-care-providers?utm_campaign=FDA%20MedWatch%20Use%20of%20Serological%20%28Antibody%29%20Tests%20for%20COVID-19&utm_medium=email&utm_source=Eloqua

More FDA Serology Guidance (FAQ page)

https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-diagnostic-testing-sars-cov-2

FDA Educational materials

https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-serological-test-validation-and-education-efforts

Please Type Your Questions in the Question Box!