



COLLEGE of AMERICAN  
PATHOLOGISTS

# Validating Laboratory Testing During a Novel Pandemic

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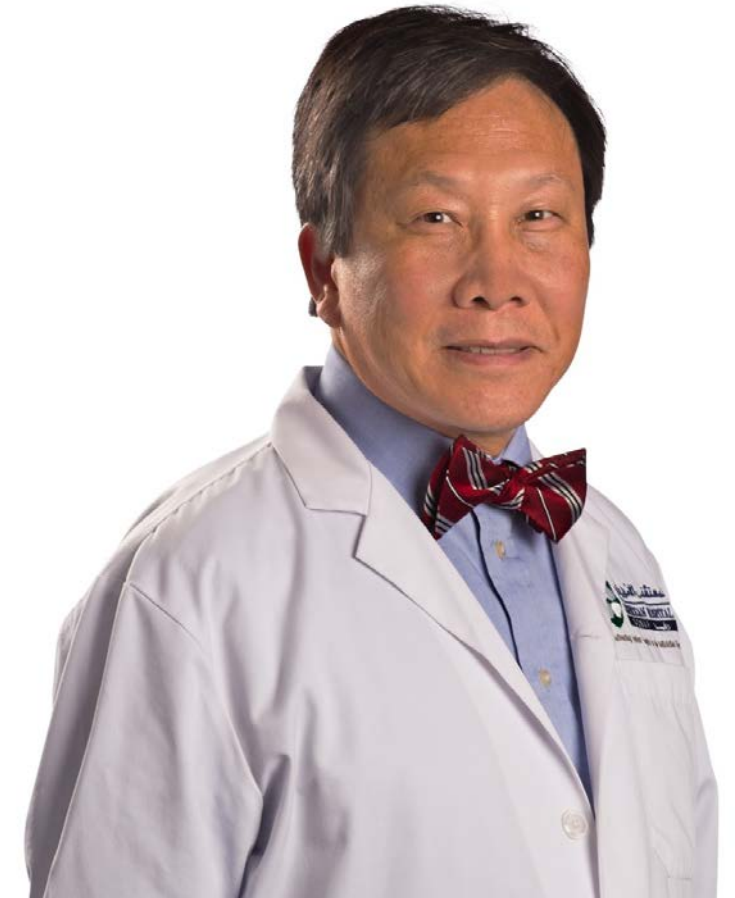
September 5, 2020

# Opening Comments

- The role of the lab has never been greater than it is today.
- High-quality, adaptable labs are foundational to a strong health care system.
- Accreditation is foundational to building a high-quality, adaptable lab.
- COVID-19 is an excellent case study.

# Today's Presenter: Dr. Aaron Han, MD, PhD, FCAP

- **Adjunct Professor of Pathology at Mohammed bin Rashid University (MBRU) School of Medicine**
- **CAP Deputy International Commissioner for the United Arab Emirates**
- **Member of the CAP Point of Care Committee**



# The problem with novel diseases

**wikiHow**

Article Edit

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## How to Build an Airplane

Co-authored by **wikiHow Staff** · [References](#)  
Updated: March 28, 2020

For some people, building and flying your own plane is a satisfying personal experience. Constructing your own plane is legal in most countries and you don't need to know any skills to begin. You can start by purchasing a kit online and getting involved with aviation organizations. Once you're done building, register your plane with your government's aviation board. Then, you can enjoy cruising the skies in a plane customized to your liking. This article is for building full scale aircraft. To build a model airplane, check out some different wikiHow articles.

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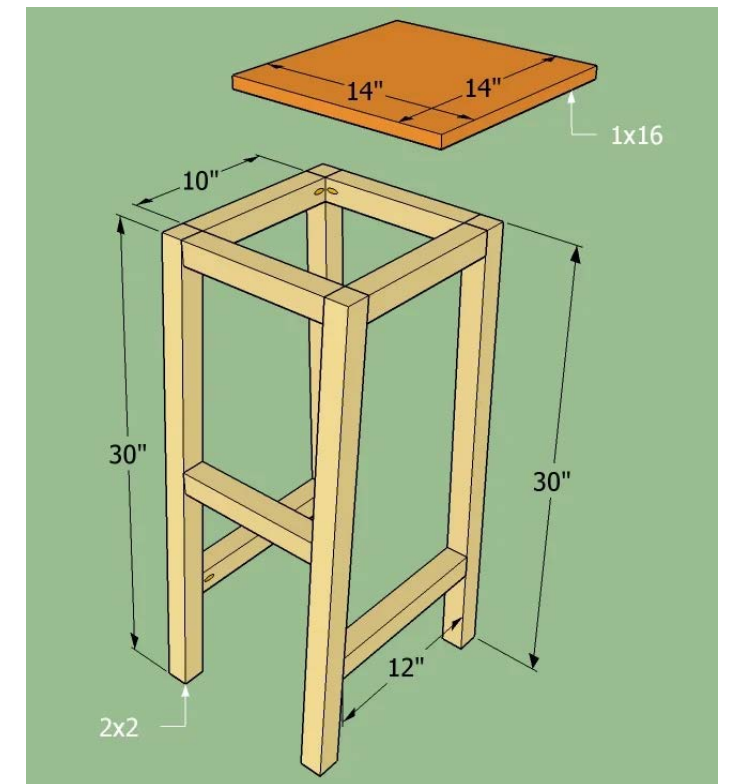
Graphic Source: <https://www.youtube.com/watch?v=Y7XW-mewUm8>

# What will be addressed during our session

- **Development of COVID testing**
  - Types of tests
  - Differences between tests
- **Thoughts on the near future**
  - Serology and convalescent serum
  - Overlap with influenza season
- **Pandemic preparedness via accreditation rigor**
- **Q&A**

# Usual lab testing framework

- Performance characteristics
- Phases of testing and impact on results
- External quality assurance (EQA), proficiency testing (PT)
- Quality control (QC)
- Validation and verification



Graphic Source: <https://www.howtospecialist.com/wp-content/uploads/2012/09/Building-a-stool.jpg>

# FDA marking during the pandemic

- Emergency Use Authorization (EUA)



Graphic Source: <https://emmainternational.com/fdas-emergency-use-authorization/>

[Home](#) > [Laboratory Improvement](#) > [Proficiency Testing](#) > SARS-CoV-2 Proficiency Testing Programs

# SARS-CoV-2 Proficiency Testing Programs

As laboratories expand patient testing capabilities for detection of or exposure to the novel coronavirus (SARS-CoV-2), we have introduced new proficiency testing (PT) programs to support your efforts.



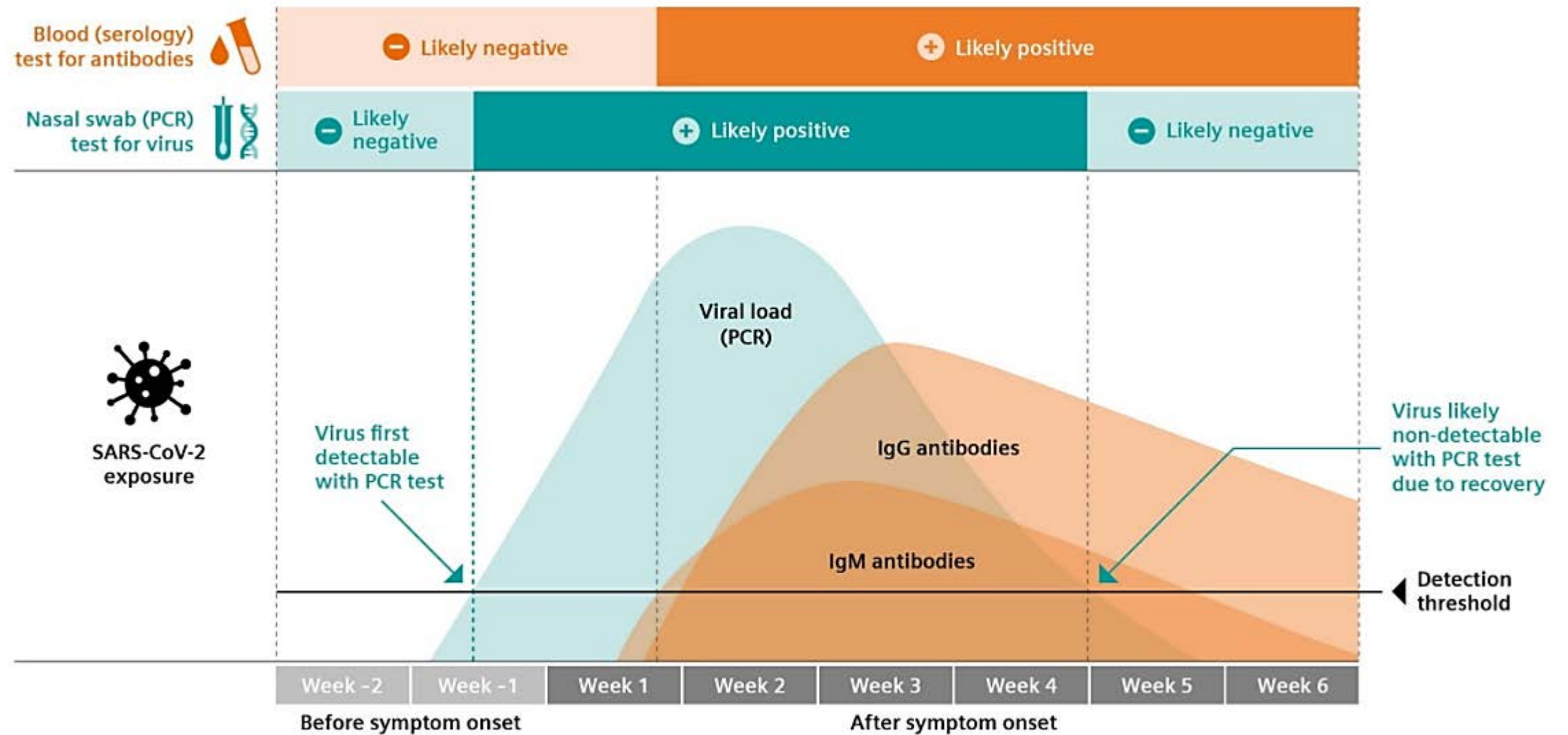
## Enroll Today

Place your order today to ensure material availability.

[Order SARS-CoV-2 Serology \(COVS\)](#)[Order SARS-CoV-2, Molecular \(COV2\)](#)

# Types of tests

- Molecular
- Serology



Graphic Source: [https://www.siemens-healthineers.com/en-us/laboratory-diagnostics/assays-by-diseases-conditions/infectious-disease-assays/covid-19-laboratory-testing#Why\\_Antibody\\_Tests?](https://www.siemens-healthineers.com/en-us/laboratory-diagnostics/assays-by-diseases-conditions/infectious-disease-assays/covid-19-laboratory-testing#Why_Antibody_Tests?)

# Gold standard is PCR

- Limitations are
  - Pre-analytical
  - Contamination
  - Relapse and detection of dead virus
  - Number of probes in the primer set

**South Korea says recovered coronavirus patients who tested positive again did not relapse: Tests picked up 'dead virus fragments'**

Sinéad Baker Apr 30, 2020, 1:36 PM



Source: Business Insider, Apr 30, 2020. <https://www.businessinsider.com/coronavirus-south-korean-reactivated-cases-not-reinfected-experts-2020-4>

# What did the UAE do?

LIFE

## THE UAE BUILT THE SECOND LARGEST OPERATIONAL CORONAVIRUS TESTING FACILITY IN THE WORLD

The laboratory will be capable of processing tens of thousands of tests a day.

BY SCENE ARABIA - 02 Apr 2020

SHARE TWEET



Source: <https://scenearabia.com/Life/The-UAE-Built-the-Largest-Operational-Coronavirus-Testing-Facility-Outside-of-China>

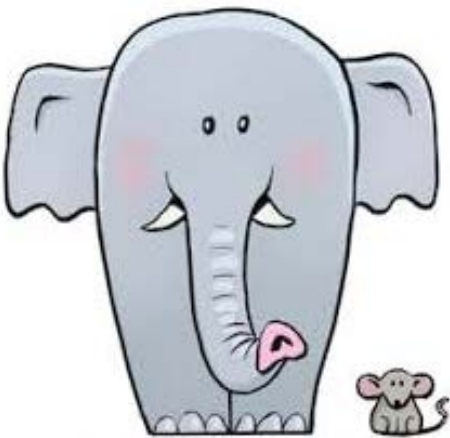
## COVID-19 UAE: Dubai conducts more than 600,000 tests

Emirate to continue increasing testing as part of relentless efforts to combat pandemic

Published: June 22, 2020 20:31  
Gulf News Report



Source: <https://gulfnews.com/uae/government/covid-19-uae-dubai-conducts-more-than-600000-tests-1.1592843566493>



Graphic Source: Shutterstock  
Image 607763987

# PCR in a suitcase – 4 hours to result



Source: Dr. A. Han

# Other rapid molecular tests are coming

- **Results in 45 minutes or less**
- **COVID only versus syndromic panel (multiple flu viruses)**
- **Saliva**
- **Self/Home sampling**

# What about the usefulness of a syndromic panel?

	COVID-	COVID+
RVP-	23	14
RVP+	60	3

**NPV 95%**

PPV 38%

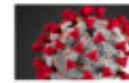
Source: Dr. A. Han, manuscript in review

# Serology

- Rapid (fingerstick)
- Non-rapid (ELISA)
- Gold standard is
  - Competent/protective serum
  - Viral assay
  - Plasma therapy

## Mayo Clinic launches test to detect COVID-19 immunity

JUNE 12, 2020 BY SEAN WHOOLEY — [LEAVE A COMMENT](#)



Mayo Clinic announced that it launched a new SARS-CoV-2 neutralizing antibody test in support of efforts to establish therapies and vaccines for COVID-19.

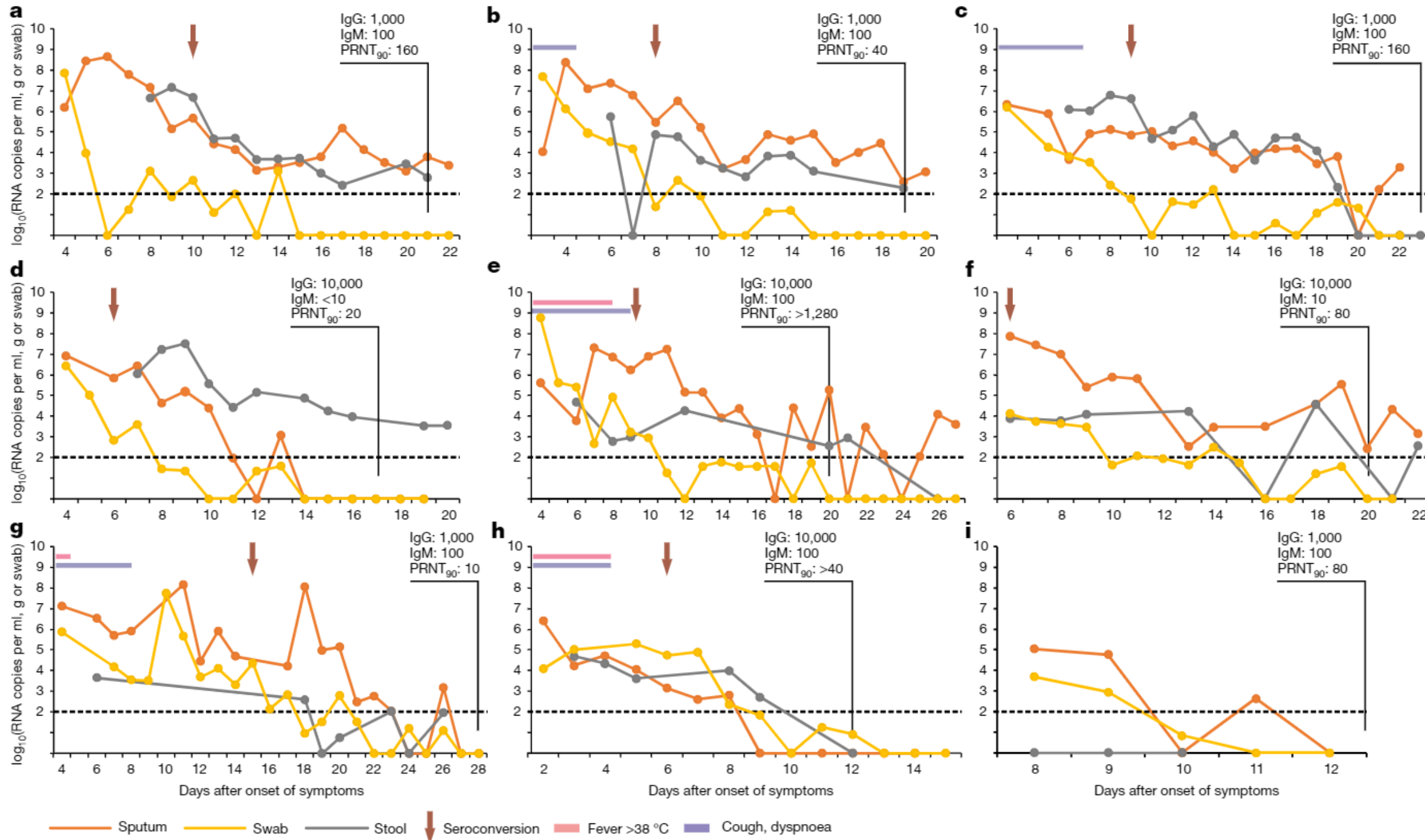
As part of the Expanded Access Program for Convalescent Plasma and other critical research efforts, Mayo Clinic intends to make the test available to select labs, blood banks and biopharma clients later this month.

Mayo Clinic designed the new test to measure the level of neutralizing antibodies against SARS-CoV-2, the virus causing COVID-19. The test provides semi-quantitative detection of total neutralizing antibodies in human serum. After infection, most will develop an immune response to COVID-19, including the production of neutralizing antibodies against the SARS-CoV-2 spike glycoprotein. However, it's currently unknown for how long the neutralizing antibodies persist after infection.

The test should only be ordered upon confirmation of prior infection and it should not be used to diagnose SARS-CoV-2 infection, according to a news release.

Source: Mass Device, June 12, 2020. <https://www.massdevice.com/mayo-clinic-launches-test-to-detect-covid-19-immunity/>

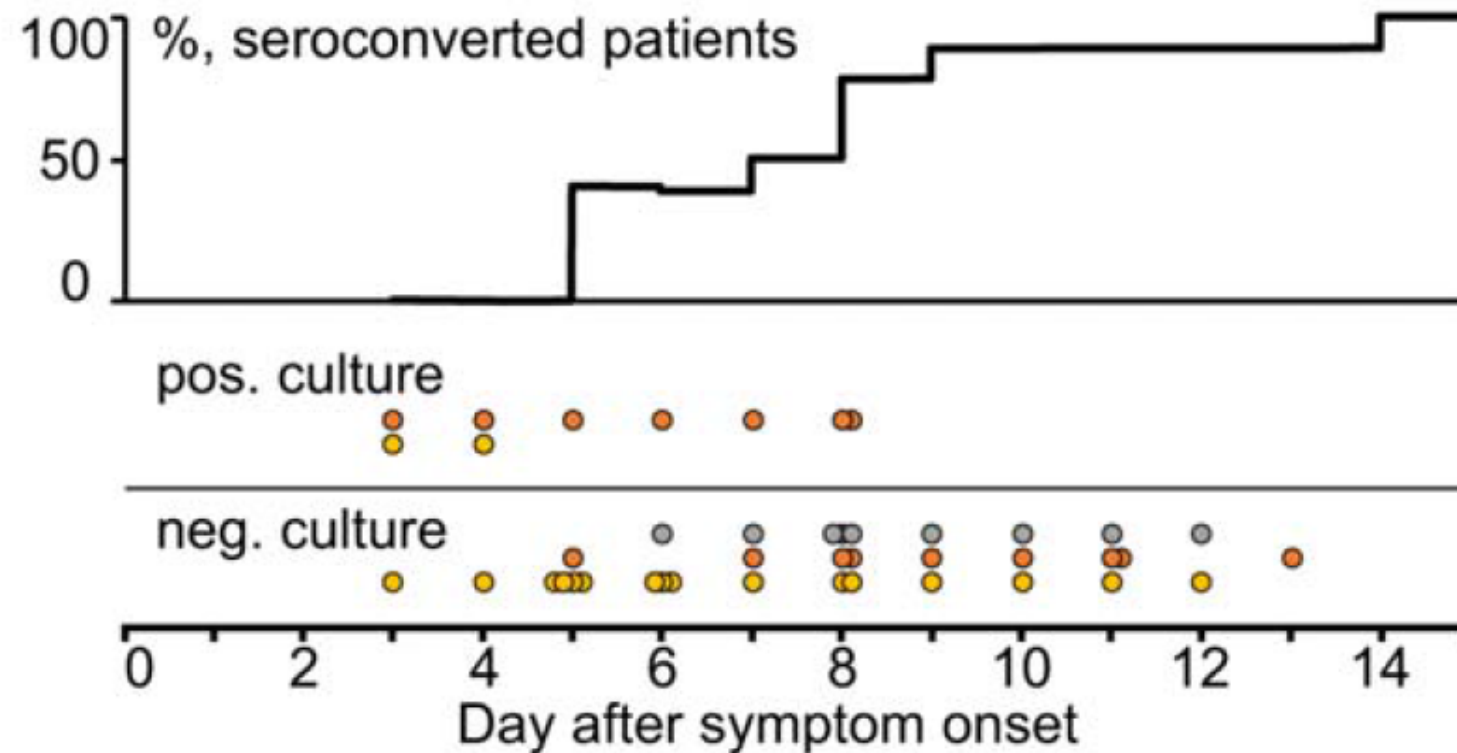
# What was Massachusetts General Hospital (MGH)'s experience?



Source:  
<https://rdcu.be/b6a1q>

# Update on COVID19 serologic testing at MGH

What we know – more as of 4/1/2020



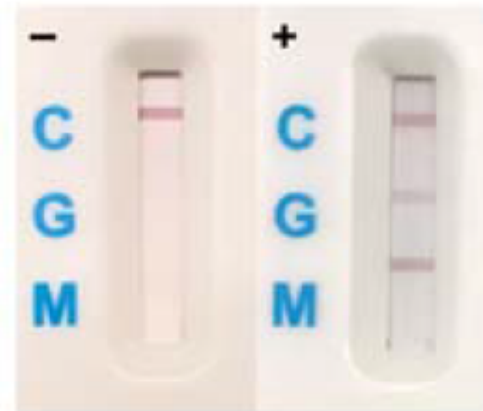
In this 9 person cohort

- Patients start to seroconvert at day 5
  - 50% seropositive by day 7
  - 100% seropositive by day 14
- Infectivity as determined by viral isolation and culture
  - Naso- and Oropharynx infectious mostly early on in disease
  - Sputum infectious most consistently from beginning through 8 days post-symptom onset
  - No live virus isolated from stool (all mild cases)

# Update on COVID19 serologic testing at MGH

## Lateral flow assays for Point-of-Care Testing

Easy to read in 10 min!

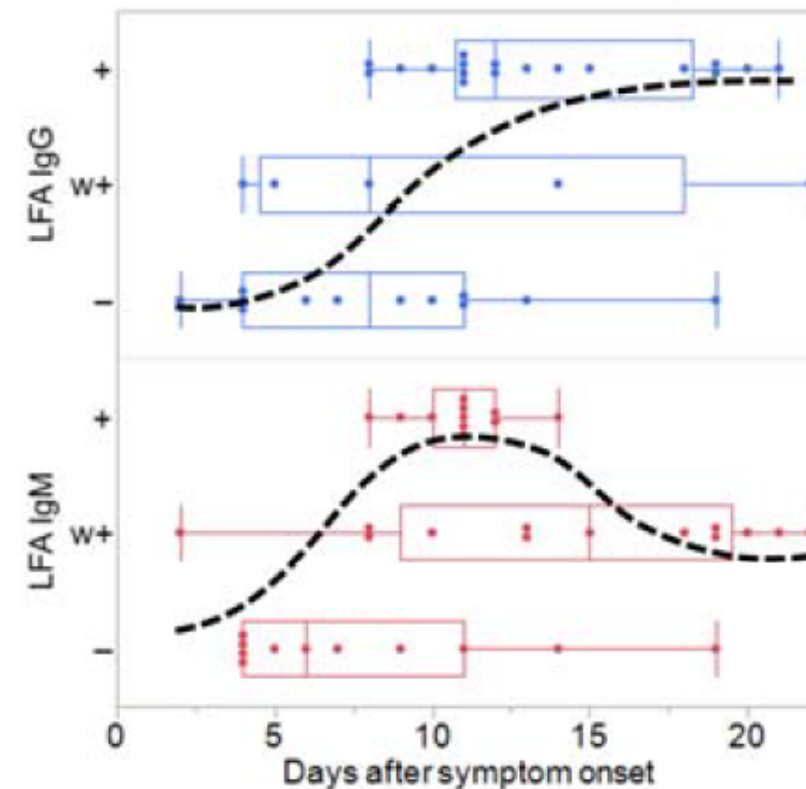


### Sensitivity of detection

Symptoms	IgM+	IgG+	IgG+ or IgM+
≤7 days	13% (1/8)	25% (2/8)	38% (3/8)
>7 days	85% (23/27)	78% (21/27)	89% (24/27)

**Specificity = 100% (0/33)**  
(includes 3 non-COVID-19 coronavirus+)

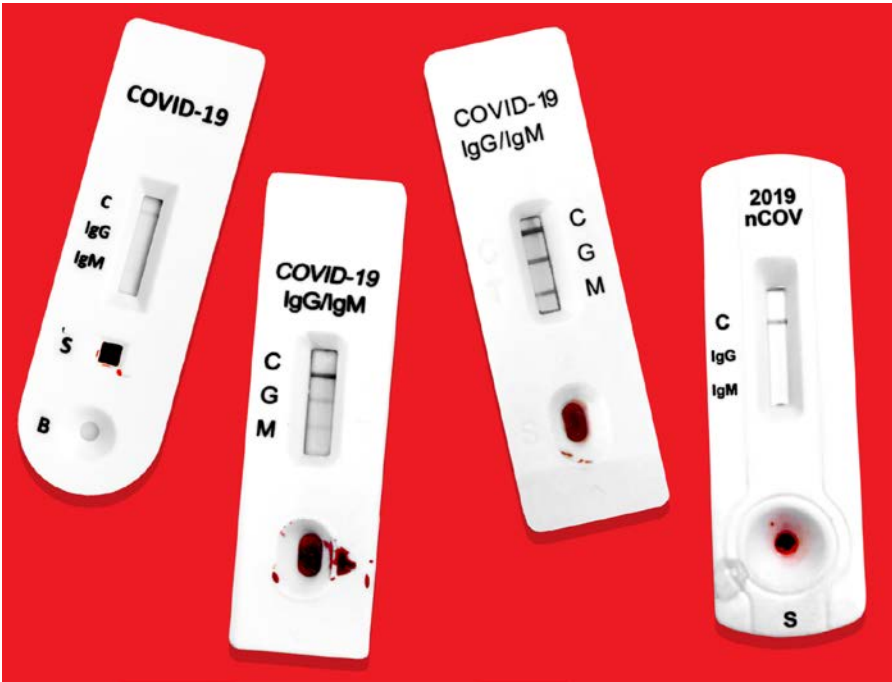
### Kinetics of positivity



\*100% sensitivity at day 12, age <80



# Not all assays are similar



Graphic Source: <https://www.bloomberg.com/news/articles/2020-05-05/coronavirus-antibody-tests-may-produce-contradictory-results>

FDA NEWS RELEASE

## Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chembio Antibody Test

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Press Announcements

For Immediate Release: June 16, 2020

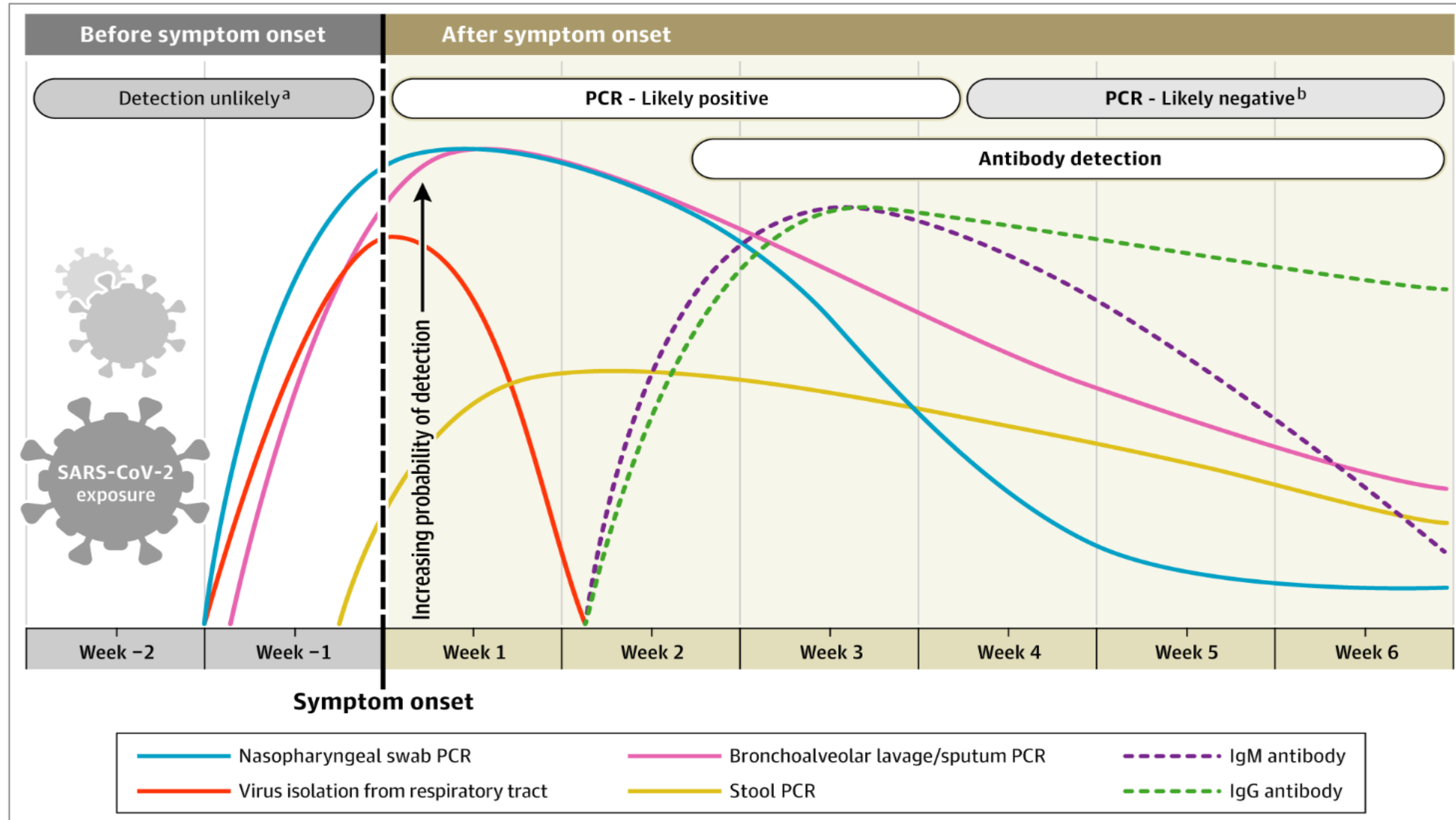
Español

Today, the U.S. Food and Drug Administration [revoked the emergency use authorization \(EUA\)](#) of the Chembio Diagnostic System, Inc. (Chembio) DPP COVID-19 IgM/IgG System, a SARS-CoV-2 antibody test, due to performance concerns with the accuracy of the test. Antibody tests, a type of serological test, can help provide information on a person’s and population’s exposure to COVID-19.

**“Since the beginning of the COVID-19 public health emergency, the FDA has balanced the urgent need for access to diagnostic and antibody tests with providing a level of oversight that helps to ensure accurate tests are being deployed,”** said Jeff Shuren, M.D., director of FDA’s Center for Devices and Radiological Health. **“By continuing to monitor authorized tests and emerging scientific evidence, we are able to make changes when appropriate – including taking action when a test’s benefits no longer outweigh its risks.**

Source: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chembio-antibody-test>










# Use of serology methods and timing



Source:  
<https://jamanetwork.com/journals/jama/fullarticle/2765837>

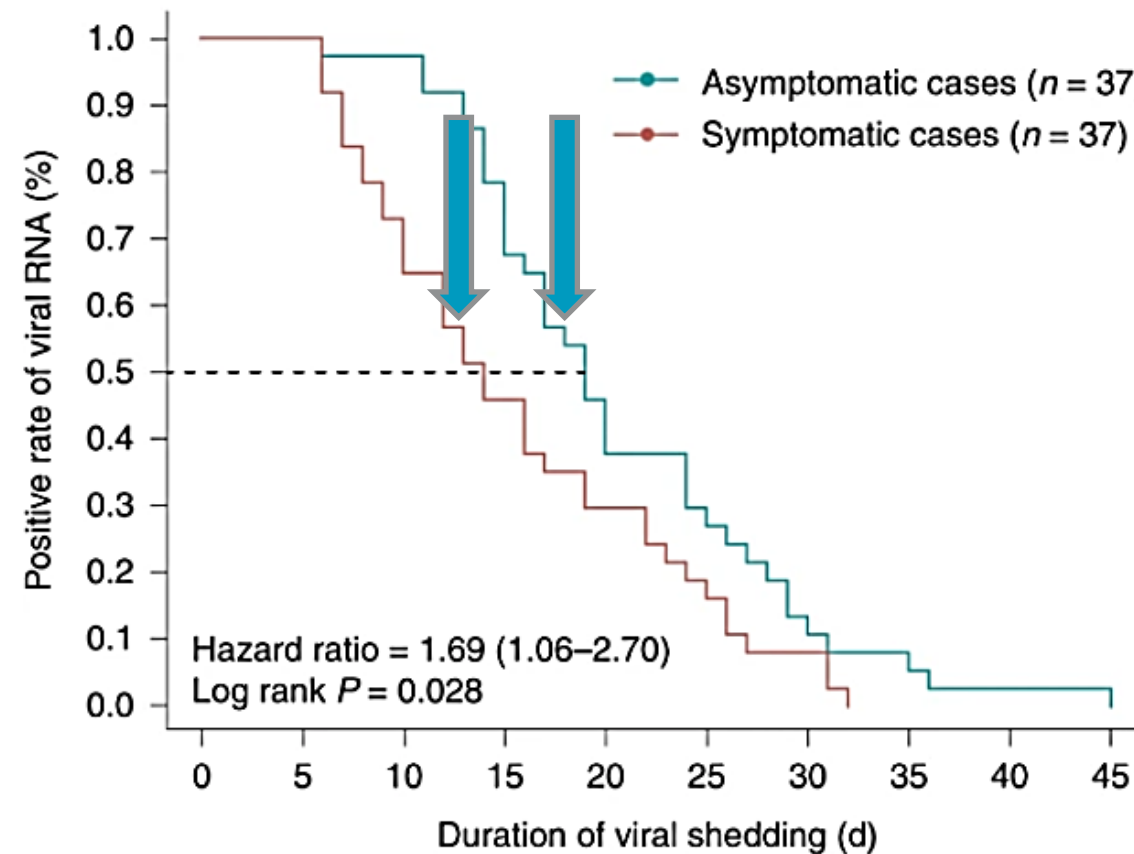
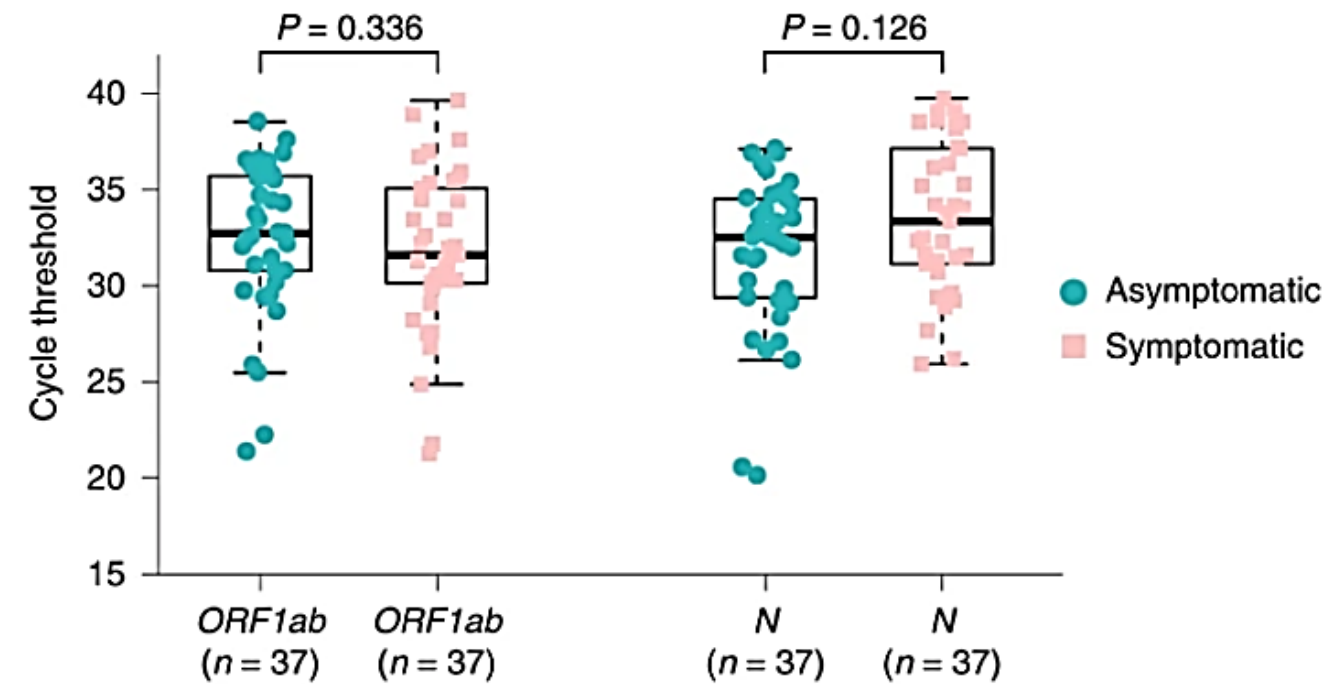


# Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections

Quan-Xin Long<sup>1,8</sup> , Xiao-Jun Tang<sup>2,8</sup>, Qiu-Lin Shi<sup>2,8</sup>, Qin Li<sup>3,8</sup>, Hai-Jun Deng<sup>1,8</sup> , Jun Yuan<sup>1</sup>, Jie-Li Hu<sup>1</sup>, Wei Xu<sup>2</sup>, Yong Zhang<sup>2</sup> , Fa-Jin Lv<sup>4</sup>, Kun Su<sup>3</sup>, Fan Zhang<sup>5</sup>, Jiang Gong<sup>5</sup>, Bo Wu<sup>6</sup>, Xia-Mao Liu<sup>7</sup>, Jin-Jing Li<sup>7</sup>, Jing-Fu Qiu<sup>2</sup>  , Juan Chen<sup>1</sup>   and Ai-Long Huang<sup>1</sup>  

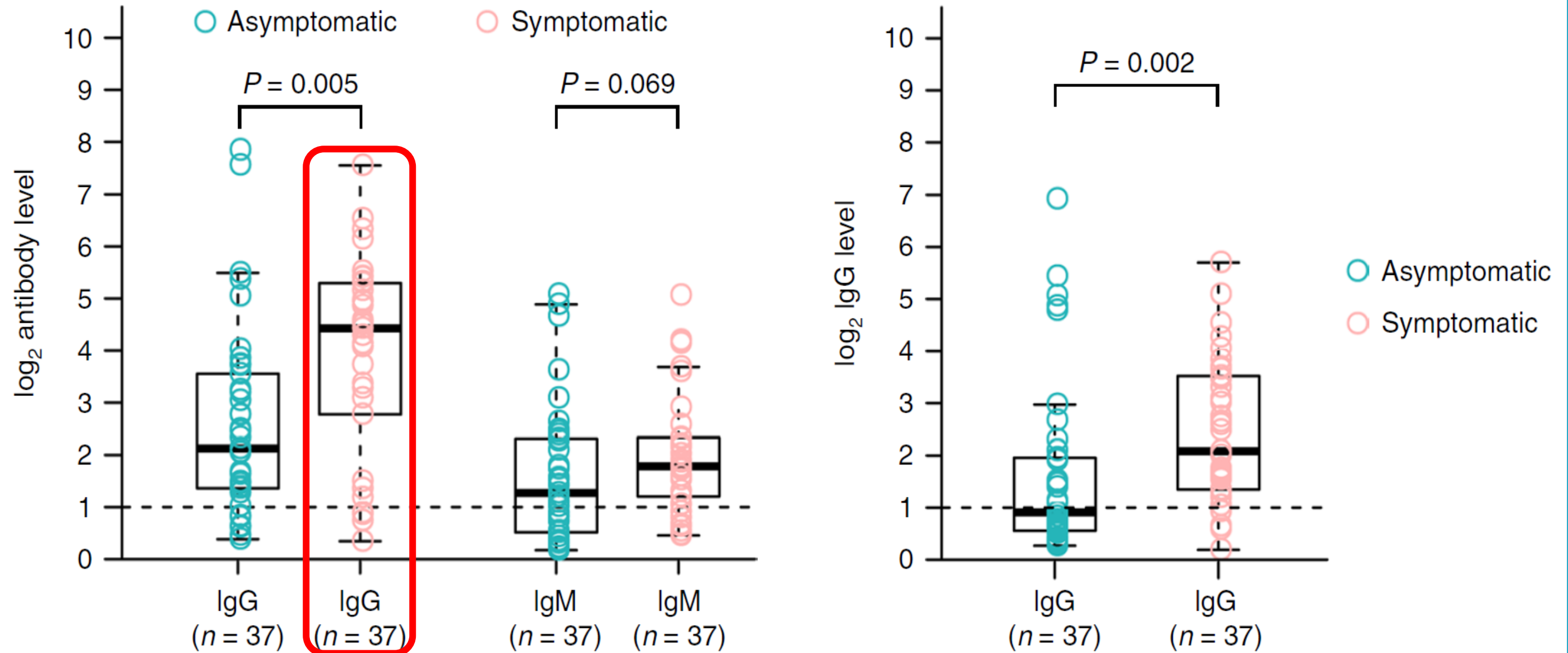
Source: <https://www.nature.com/articles/s41591-020-0965-6.pdf>

# Virology and shedding



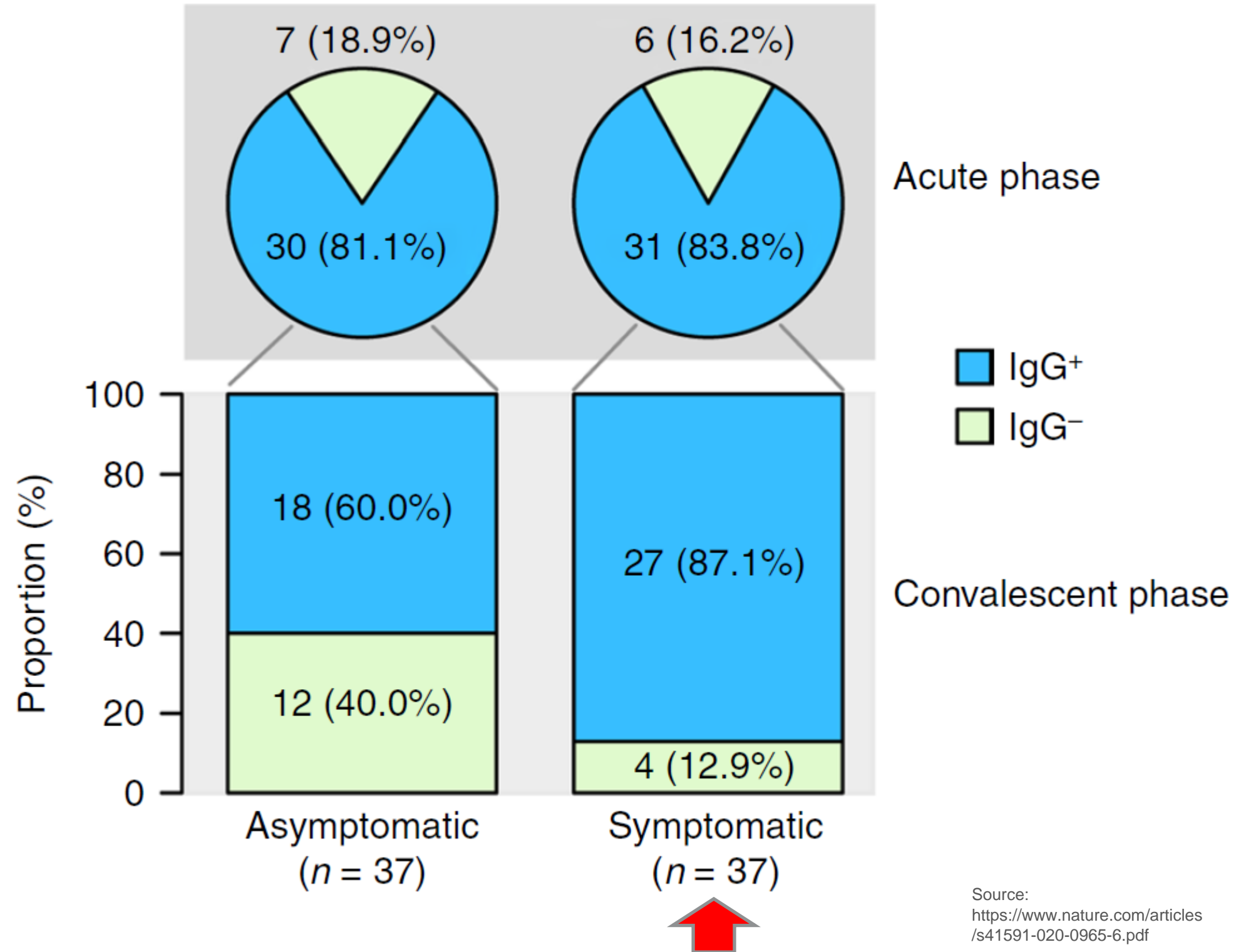
Source:  
<https://www.nature.com/articles/s41591-020-0965-6.pdf>

# Consistent higher IgG response with symptoms

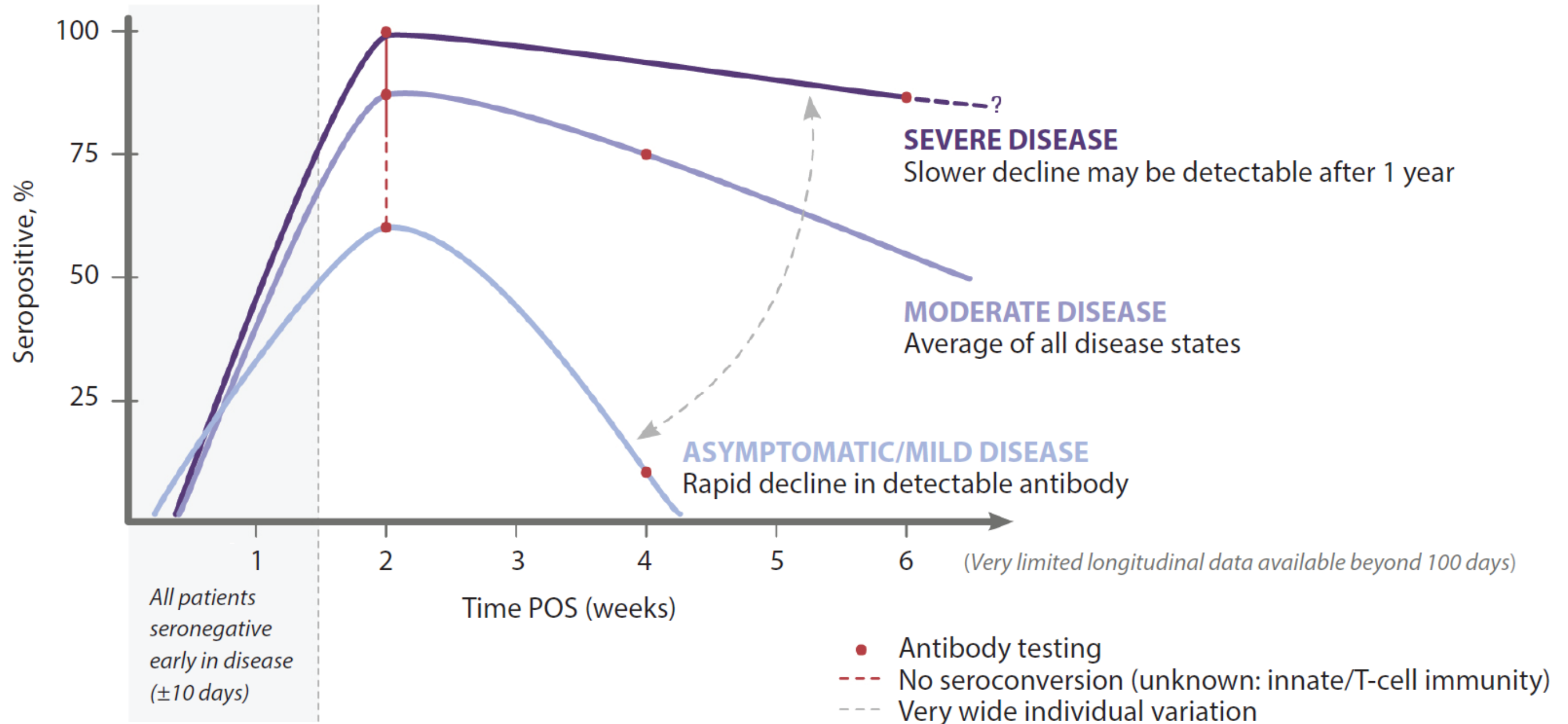


Source: <https://www.nature.com/articles/s41591-020-0965-6.pdf>

# Persistence of IgG in symptomatic patients



# Disease severity and persistence of seropositivity



Source: <http://www.samj.org.za/index.php/samj/article/view/13023/9398>

# Serology validation set

- **Ideal: Gold standard kit or titers**
- **Positive samples:**
  - PCR+ with immune response (molecular or clinical)
    - PCR clearance
    - Clinical improvement
  - PCR- clinical COVID
- **Negative samples: PCR- low risk**
  - Other Coronaviruses, HIV
- **Avoid comorbid, autoimmune patients**

# PCR negative results and serology over time

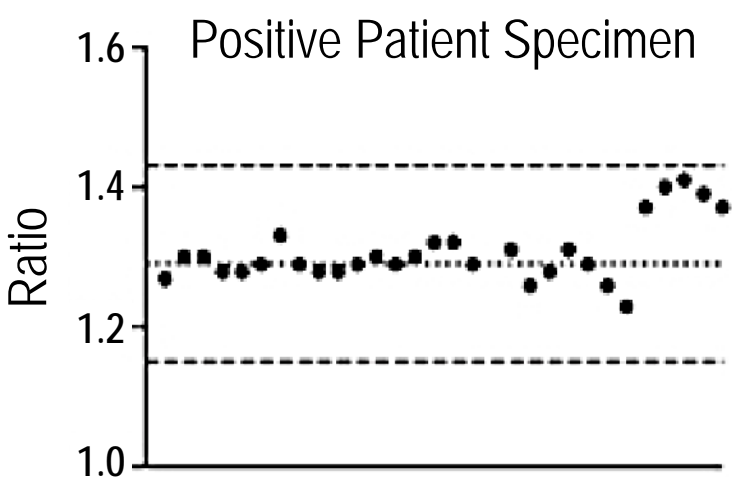
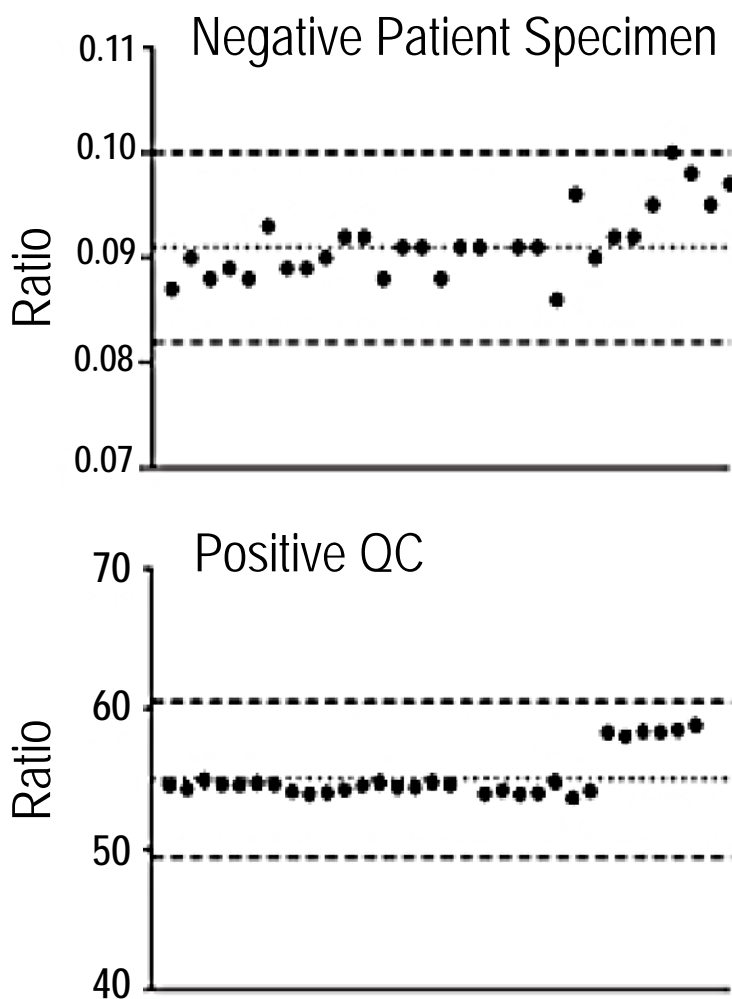


Source: Dr. A. Han

# Steps to verifying SARS-CoV-2 antibody assays



## Sample Precision Data



*Positive patient near the  
limit of detection  
 $CV = SD/Mean = <20\%$*

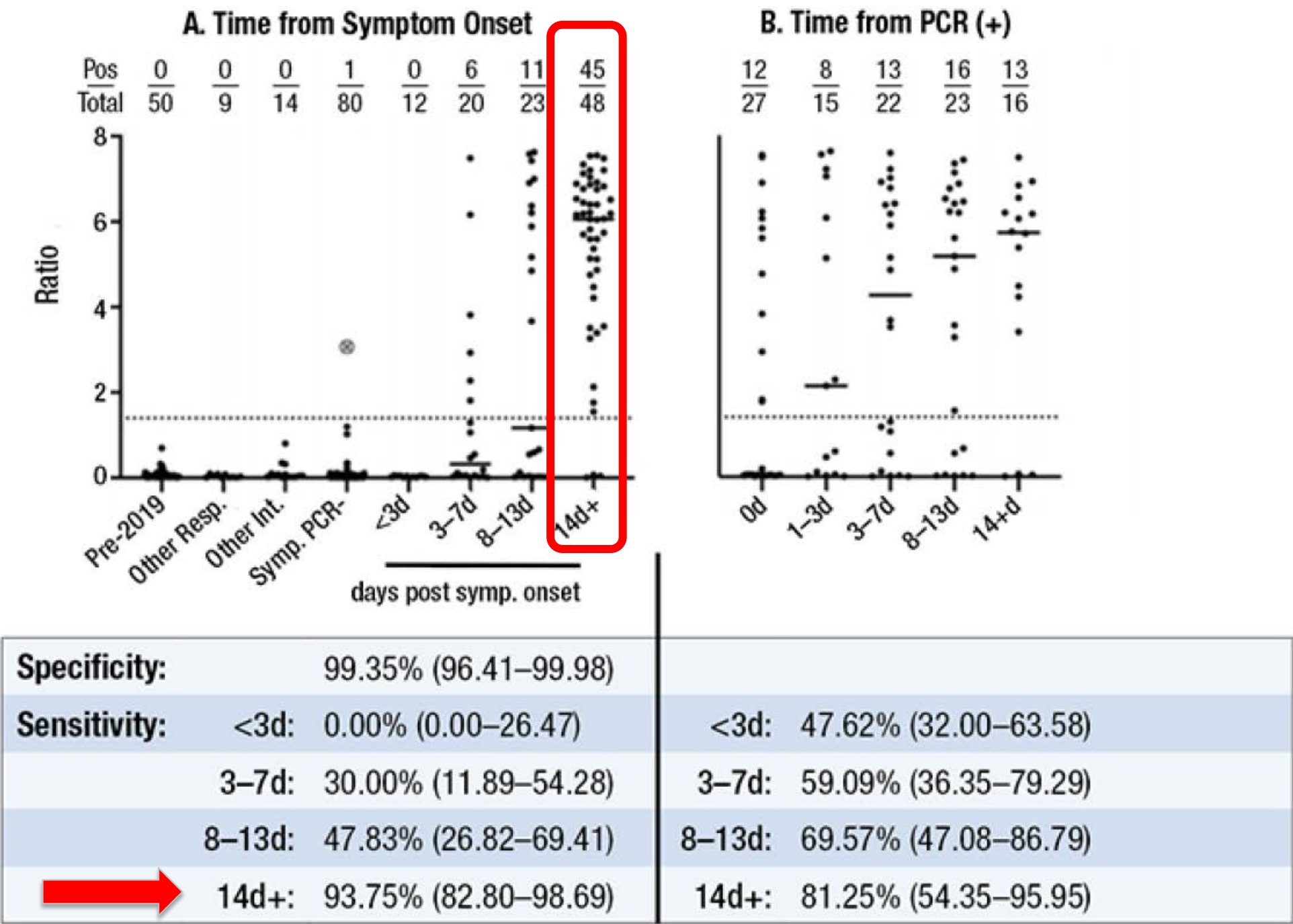
## Qualitative Analysis

Positive Percent Agreement: 60/60 = 100%  
Negative Percent Agreement: 30/30 = 100%

Courtesy of Neil Anderson, MD.

Source: <https://www.captodayonline.com/steps-to-verifying-sars-cov-2-antibody-assays/>

# Importance of timing for optimum serology testing

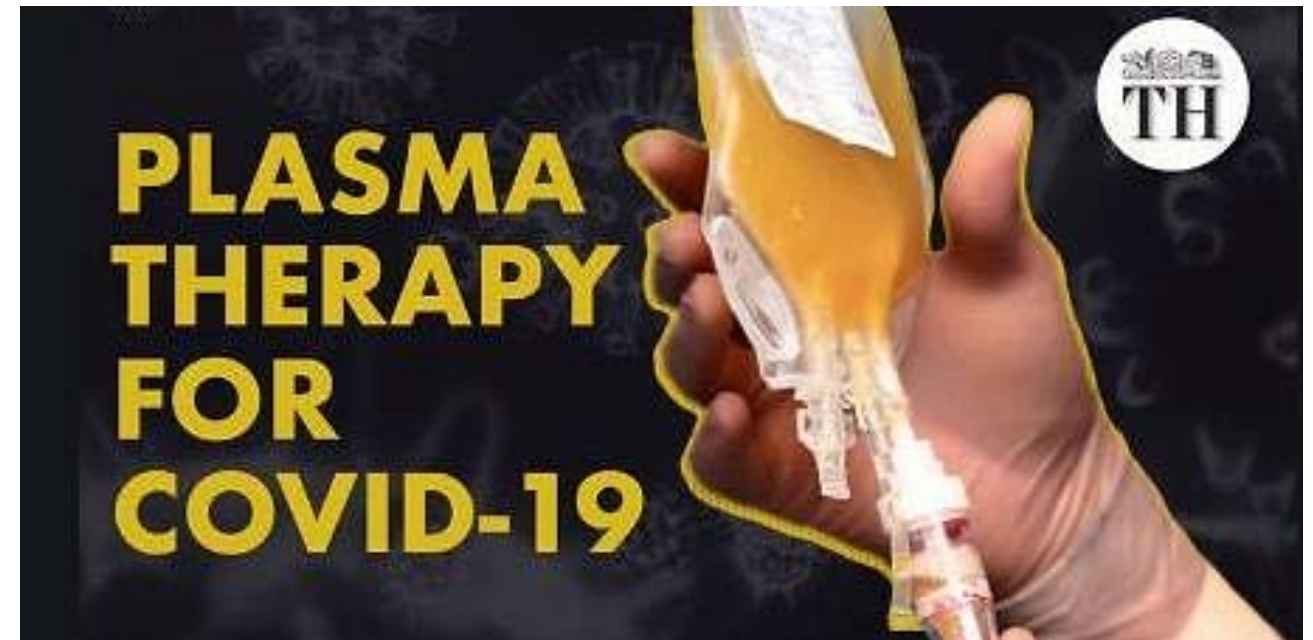


Tang MS, Hock KG, Logsdon NM, et al. Clinical performance of two SARS-CoV-2 serologic assays. *Clin Chem*. 2020;hvaa120. doi: 10.1093/clinchem/hvaa120, by permission of Oxford University Press.

Source: <https://www.captodayonline.com/steps-to-verifying-sars-cov-2-antibody-assays/>

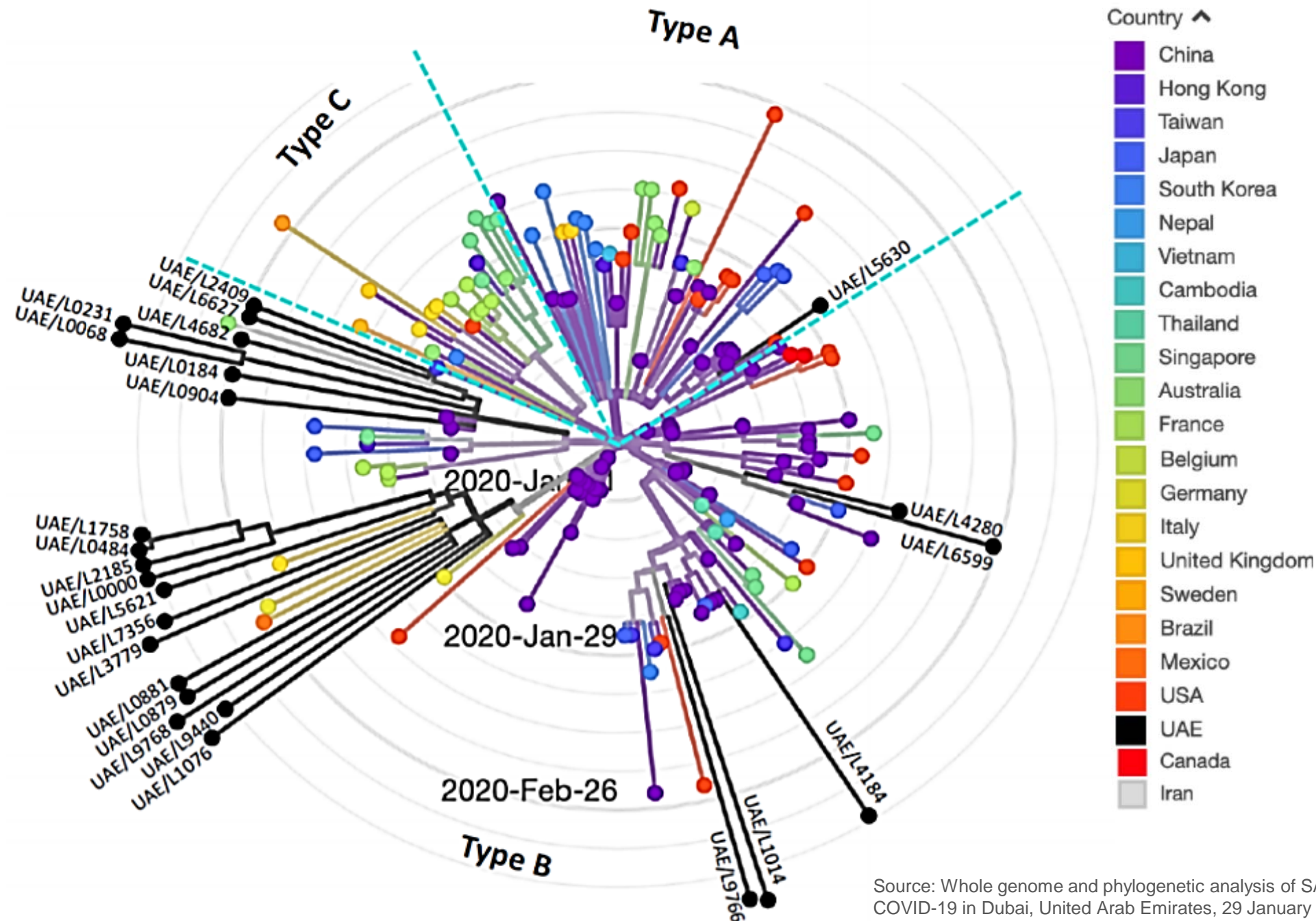
# What is serology's usefulness?

- Confirm classic cases which are PCR negative
- Epidemiology
- Immunity, need functional correlate
- Vaccine efficacy



Graphic Source: The Hindu - <https://www.youtube.com/watch?v=gd18KTRDGjs>

# NGS and sequencing in the UAE



- Radial phylogenetic tree generated from open-source tools 'Augur' and 'Auspice' (nexstrain.org)
  - 182 SARS-CoV-2 genomes used
  - 157 obtained from GISAID and 25 genomes in this study
- Filled circles = viral strains color-coded by country of origin
- Branch length for each strain = date for each sample obtained from GISAID
- Dashed black lines = boundaries of SARSCoV-2 Types A, B, and C

Source: Whole genome and phylogenetic analysis of SARS-CoV-2 strains from the index and early patients with COVID-19 in Dubai, United Arab Emirates, 29 January to 18 March 2020; Ahmad Abou Tayoun, et al. Accessed through: <https://www.biorxiv.org/content/10.1101/2020.05.06.080606v1.full.pdf>

# Summary

- **Ideal to have multiple tests**
  - PCR: early detection; identify clusters; contact tracing
  - COVID specific
    - Flu syndromic panels
    - Serology: IgM, IgG
- **Other diagnostic tests**
  - CBC: neutrophil to lymphocyte ratio (NLR)
  - ESR
  - CXR: ground glass opacities (GGO)
  - Temperature and O<sub>2</sub> saturation

# New tests

- Saliva
- T-cell response
- Laser
- Canine



Graphic source: <https://www.bbc.com/news/uk-52686660>

# COM.40300 and COM.40350

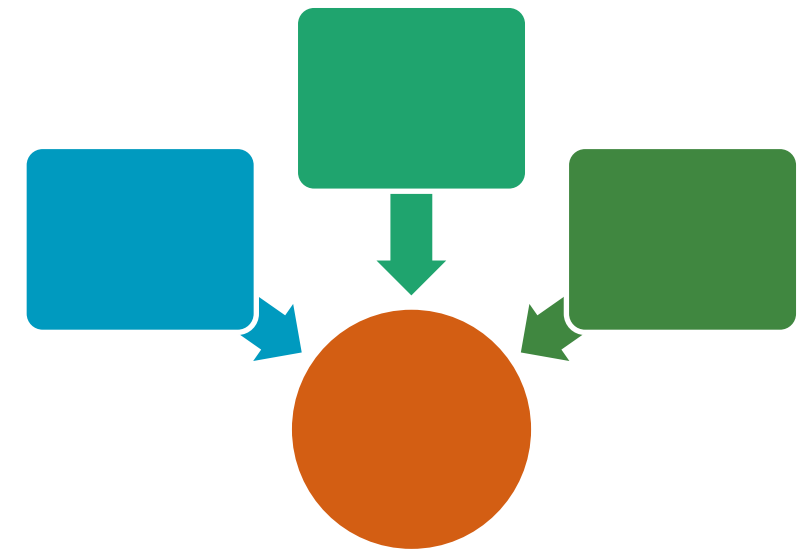
## Test method validation/verification

- Clarified method performance specifications to be verified/validated based on the type of testing performed

Requirement	Analytical Accuracy	Analytical Precision	Reportable Range	Analytical Sensitivity	Analytical Specificity
<b>COM.40300</b> (FDA-cleared or approved – Verification)	X	X	X		
<b>COM.40350</b> (Modified FDA-cleared or approved and LDTs – Validation)	X	X	X	X	

# Role and value of the lab in a novel pandemic

- **Quality and timeliness of results**
- **Know the questions that are and need to be addressed**
- **Know the limitation of your tests**
- **Have a multipronged approach**



# CAP accreditation rigor – benefits in a pandemic

- **Provides consistent procedural guidance**
  - Confidence that your staff is competent as a result of rigorous competency assessment requirements
  - Clear guidance on verification and validation of tests
- **2020 checklist requirement includes enhanced safety features for infectious pathogens**
  - New requirement in the Lab General (GEN) checklist
  - Enhancements to the bloodborne pathogen section
- **Running PT/EQA provides benchmarking opportunities**
  - Capabilities aligned with the industry
  - Large peer groups
  - Educational opportunities for the laboratorians



## Recent Updates on COVID-19



### Additional Information

[COVID-19 Information](#)

[Answers to Your COVID-19 Questions](#)

### September 3, 2020

- The CAP's Microbiology Committee updates its COVID-19 topic center with guidance on screening and surveillance [Visit here](#)
- We hear you: CAP Responds to Your COVID-19 Questions [Read the Q & A](#)
- CAP Informatics and Pathology Electronic Reporting (PERT) Committee update answers to questions about COVID-19 reporting requirements [See here](#)

### August 28, 2020

- The CAP Demands Rationale from CDC on COVID-19 Testing Guidance [Learn more](#)
- The CAP Opposes HHS Lab Penalties and for COVID-19 Reporting Requirements [Read here](#)
- CAP Informatics and Pathology Electronic Reporting (PERT) Committee answer questions about COVID-19



### New PT Program for SARS-CoV-2 Serology

Evaluate the accuracy of antibody testing—report results for qualitative and quantitative methods for total, IgG, IgM, and IgA antibodies.

[See Details and Order »](#)

# References

- Sources: WHO, CDC, CAP, Mayo; will change over time; vaccine, mutations, etc.
- Sources indicated when not CAP
- <https://www.nejm.org/doi/full/10.1056/NEJMoa2002032>

**Thank you for your participation and interest.**



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**For questions, email: [international@cap.org](mailto:international@cap.org).**