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Understanding COVID-19 Testing for CV Specialists: Small Words with Big Pictures

July 27, 2020

Speakers

- Edward Fry, MD, FACC, Session Moderator
- Emily Hyle, MD
- Bernard Macatangay, MD
- Steven Woloshin, MD

Presenter Disclosure Information

- Edward Fry, MD, FACC, Session Moderator
  - Nothing to disclose
- Emily Hyle, MD
  - I am a co-author at UpToDate.com on an unrelated topic.
- Bernard Macatangay, MD
  - Nothing to disclose
- Steven Woloshin, MD
  - Nothing to disclose

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SARS CO-V BASICS: THE VIRUS AND THE ANTIBODY RESPONSE

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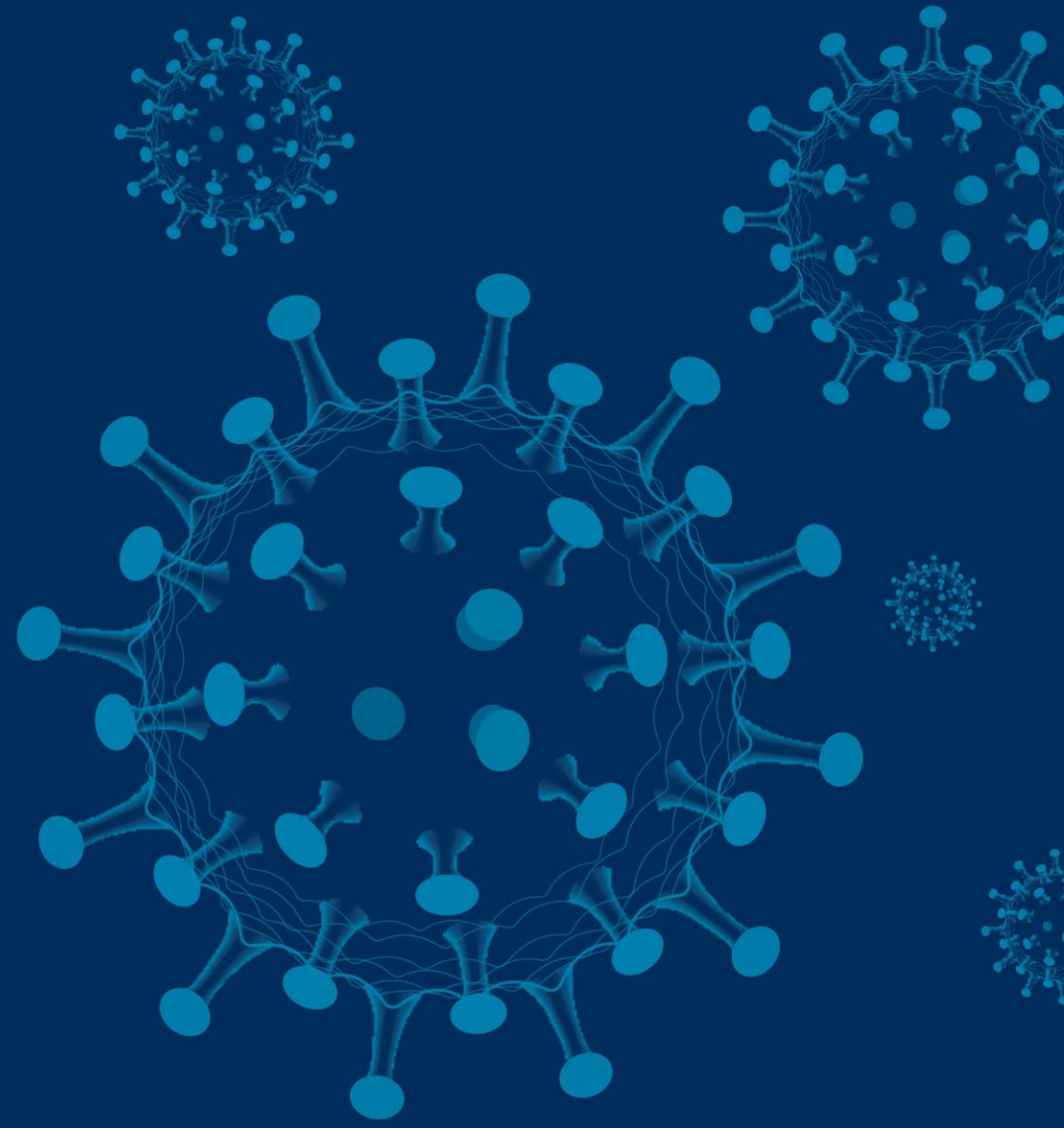

Coronaviruses and SARS CoV-2

Table 1. Human coronaviruses.

Virus	Genus	Disease	Discovered
CoV-229E	Alpha	Mild respiratory tract infection	1967
CoV-NL-63	Alpha	Mild respiratory tract infection	1965
CoV-HKU-1	Beta	Mild respiratory tract infection; pneumonia	2005
CoV-OC43	Beta	Mild respiratory tract infection	2004
SARS-CoV	Beta	Human severe acute respiratory syndrome, 10% mortality rate	2003
MERS-CoV	Beta	Human severe acute respiratory syndrome, 37% mortality rate	2012
SARS-CoV-2	Beta	Severe acute respiratory infections, <2% mortality rate	2019

- Enveloped RNA viruses
- With spiked glycoprotein embedded in envelope
- Inter- and intra-species transmission plus genetic recombination contribute to emergence of new coronavirus strains

Loeffelholz and Tang 2020
Emerg Microbes Infect.

Shereen et al. 2020
J Adv Res.

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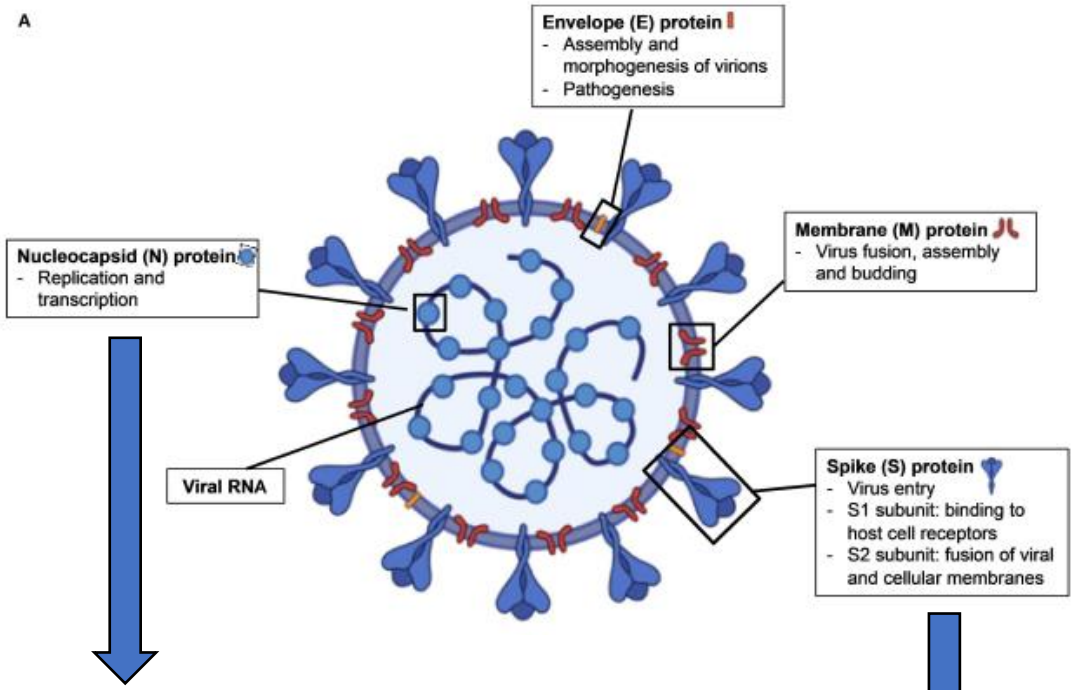
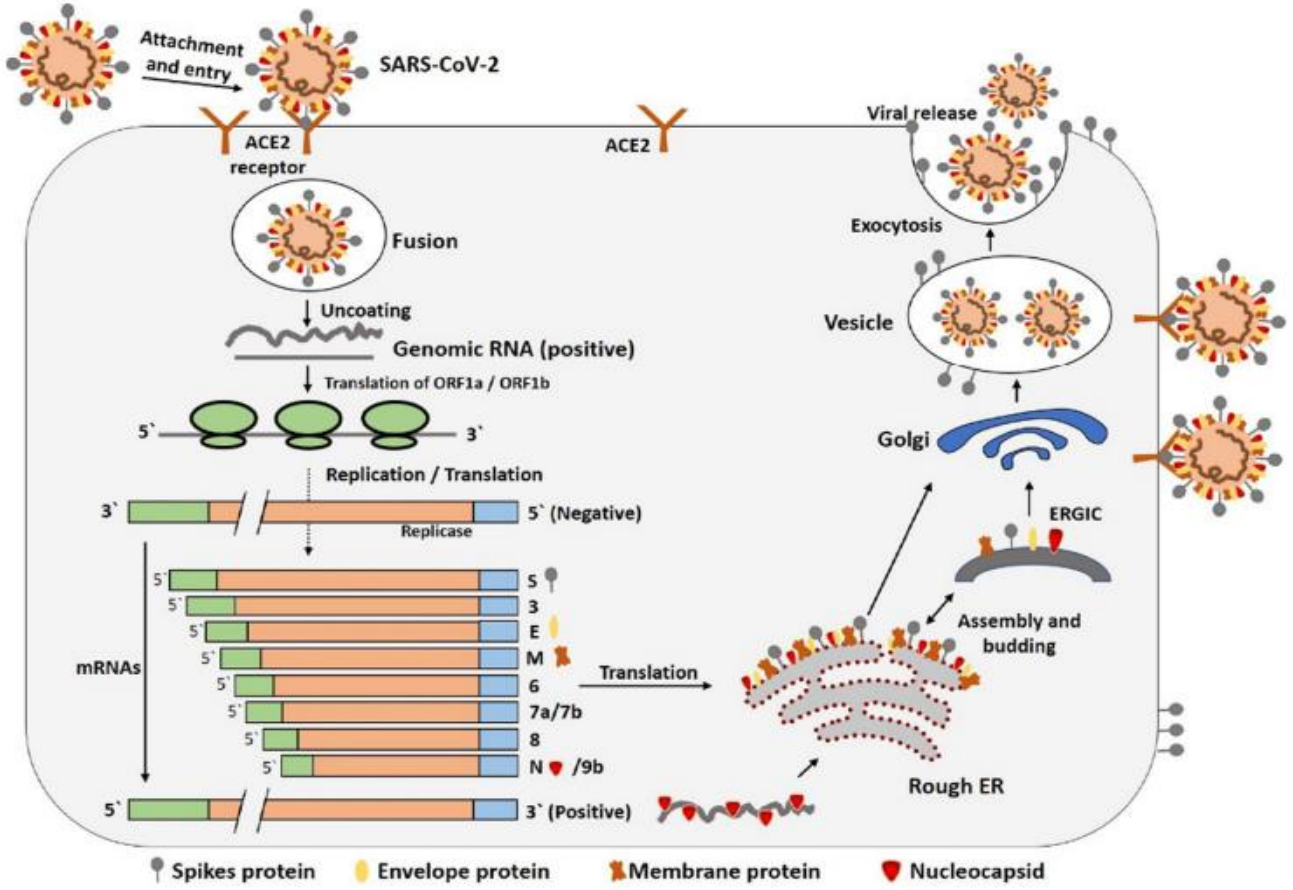
SARS CoV-2 Life cycle



Antibody Target

Antibody Target



Lee et al. 2020
Front Immunol.

Shereen et al. 2020
J Adv Res.

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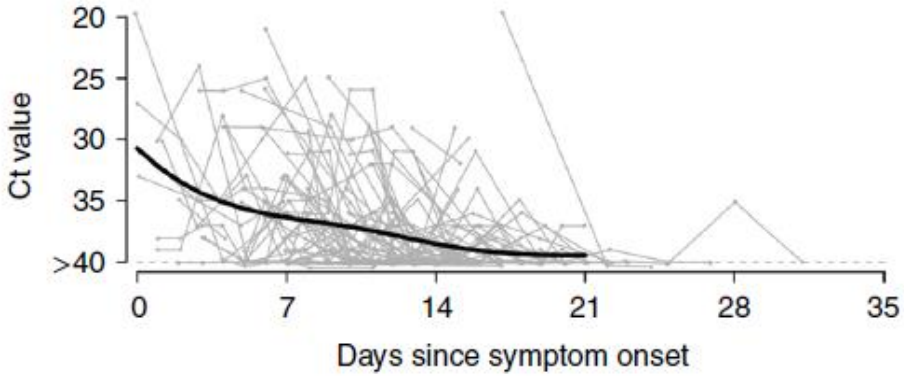
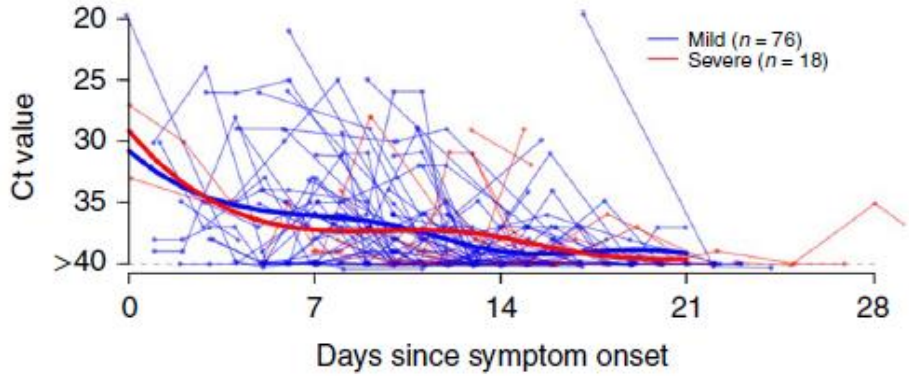
SARS CoV-2 Shedding





- Although there is a lot of variability in viral shedding, likelihood of recovering replication competent virus declines after onset of symptoms.
- Epidemiologic and virologic evidence support transmission from people who are “pre-symptomatic” and asymptomatic
- 95% of specimens without replication competent virus 15d after symptom onset

He et al. 2020
Nat Med.

Furukawa et al. 2020
Emerg Infect Dis.

CDC COVID-19 site

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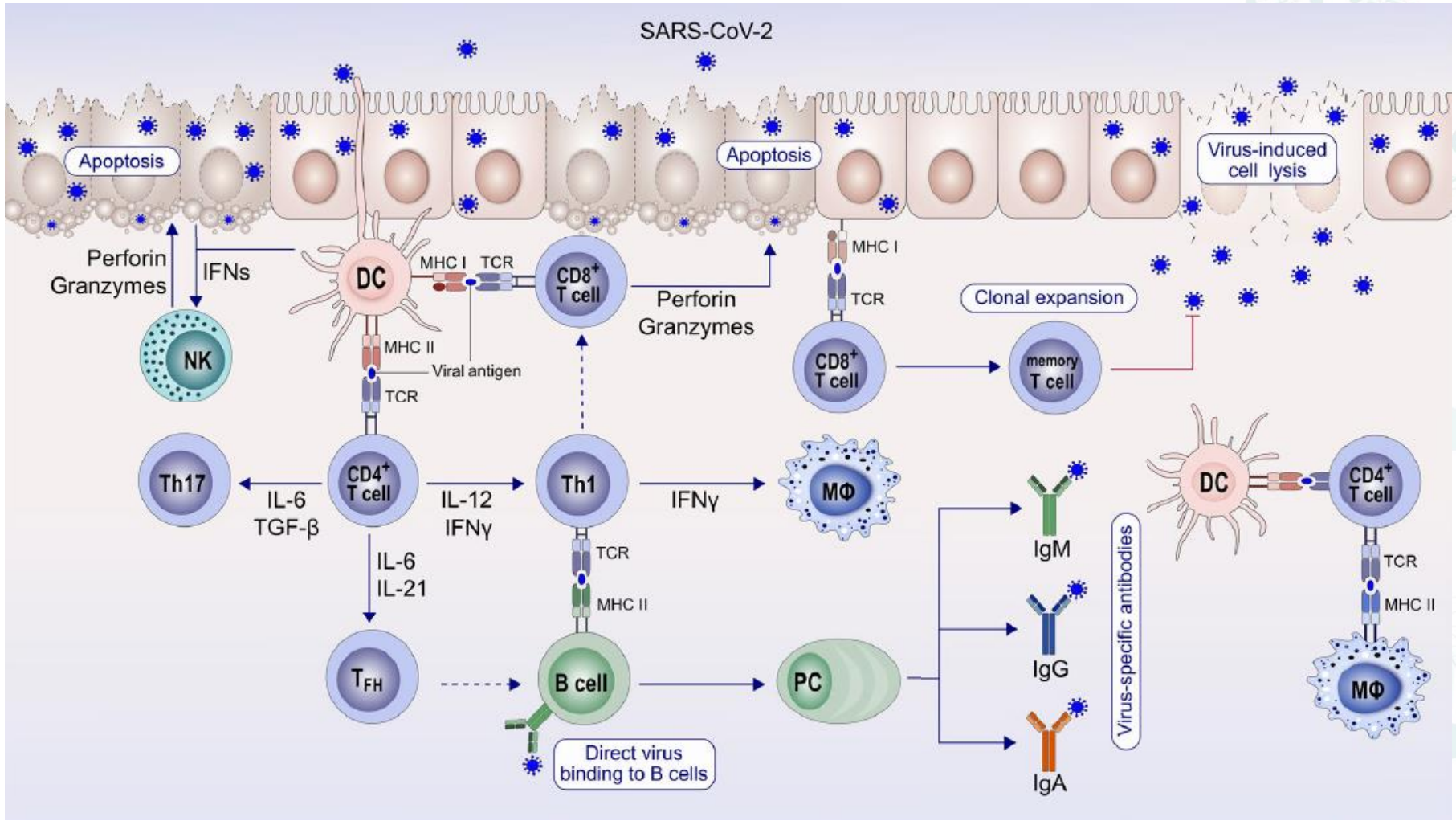
Immune Response to SARS CoV-2

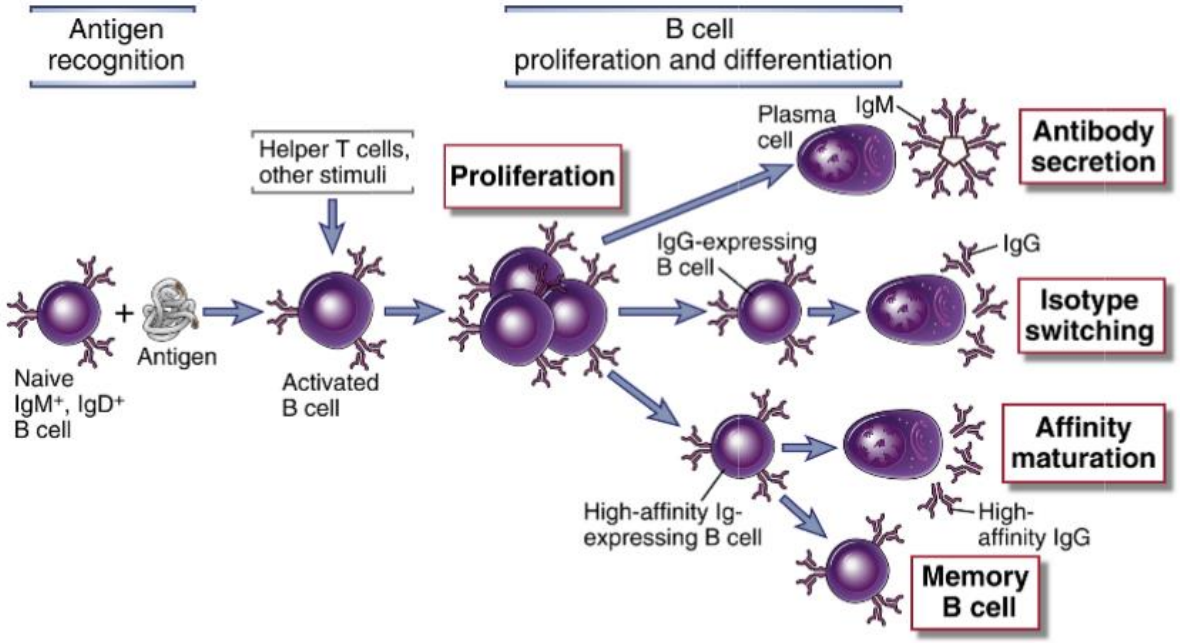


- Innate immune response (sensing of viral RNA – first line of defense)
- Adaptive/Cellular: T cell response
- Adaptive/Humoral: B cell response → antibodies

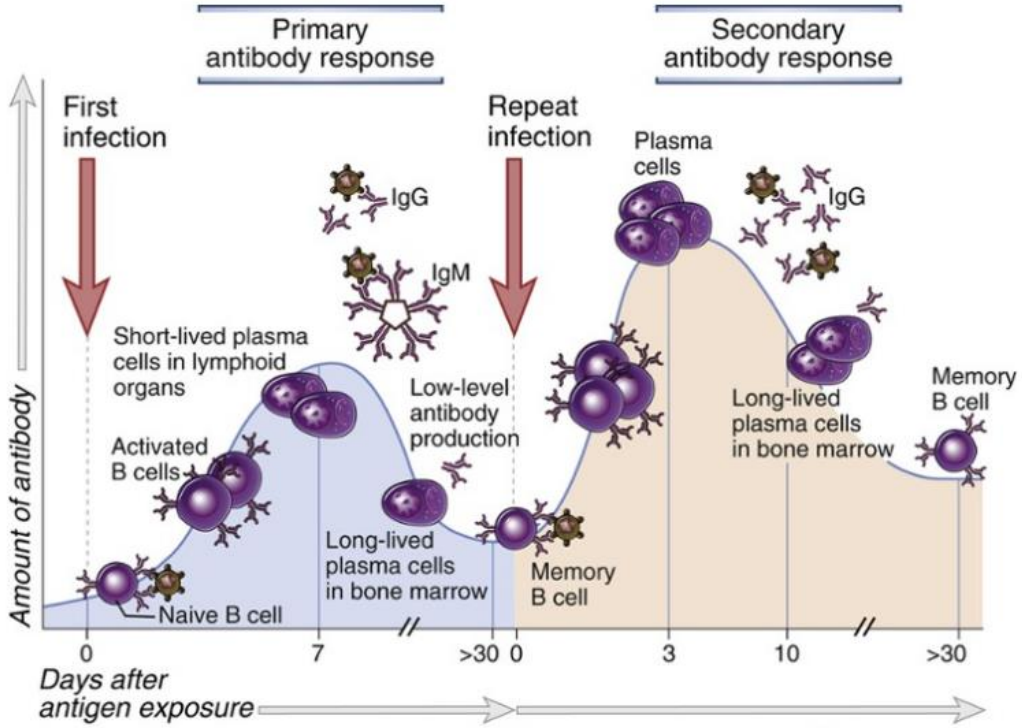
Azkur et al. 2020
Allergy

Vabret et al. 2020
Immunity

Ab response: Overview



Neutralizing Abs recognize epitopes that can eliminate infective virus vs non-neutralizing Abs which binds to the pathogen but does not affect infectivity

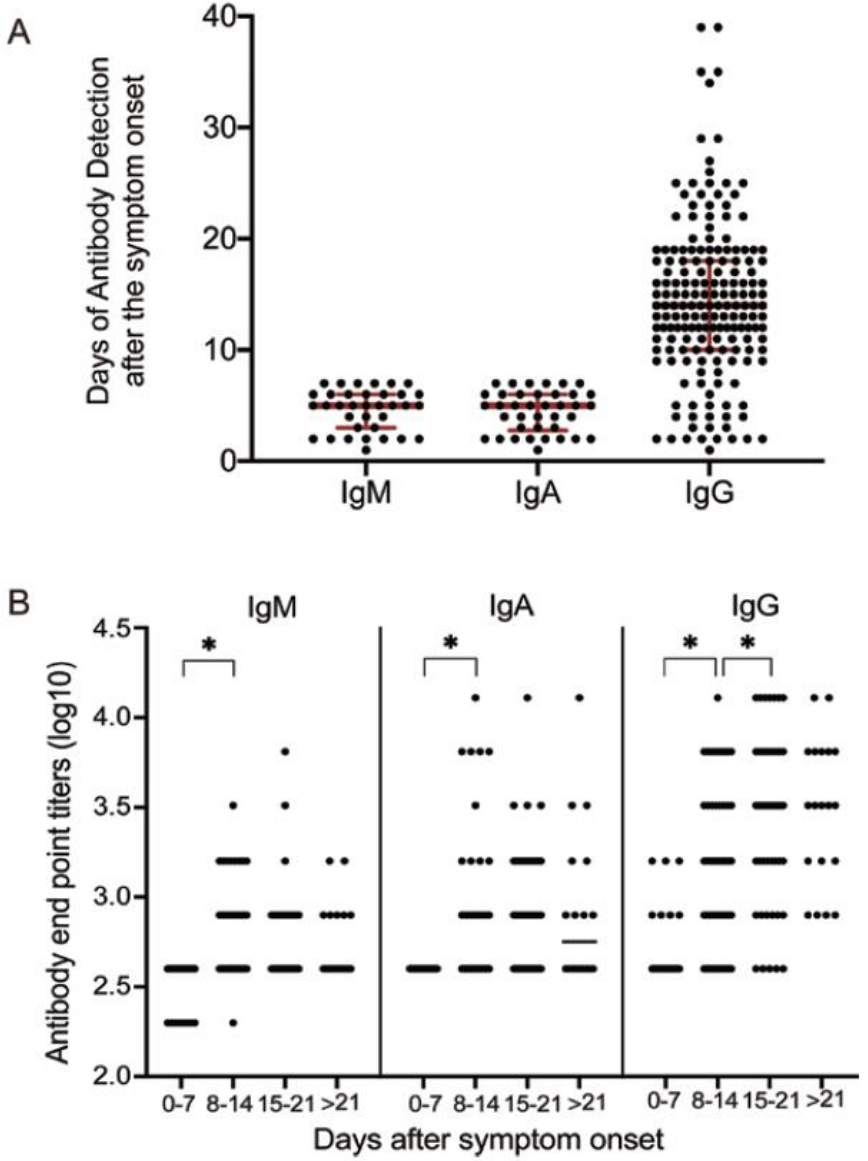


Feature	Primary response	Secondary response
Peak response	Smaller	Larger
Antibody isotype	Usually IgM > IgG	Relative increase in IgG and, under certain situations, in IgA or IgE
Antibody affinity	Lower average affinity, more variable	Higher average affinity (affinity maturation)
Induced by	All immunogens	Mainly protein antigens

Abbas et al. ed.
Cellular and Molecular Immunology

Ab responses in COVID19

- Ab <40% within 1-week of symptom onset (Zhao et al.)
- Increased to 100% (IgM 94.3%) and (IgG 79.8%) by day 15 (Zhao et al.)
- Median duration of IgM/IgA detection was 5d at 85.4% and 92.7% positive rate
- Median for IgG was 14d at 77.9% positive rate (Guo et al.)



Zhao et al. 2020 Clin Infect Dis.

Guo et al. 2020 Clin Infect Dis.

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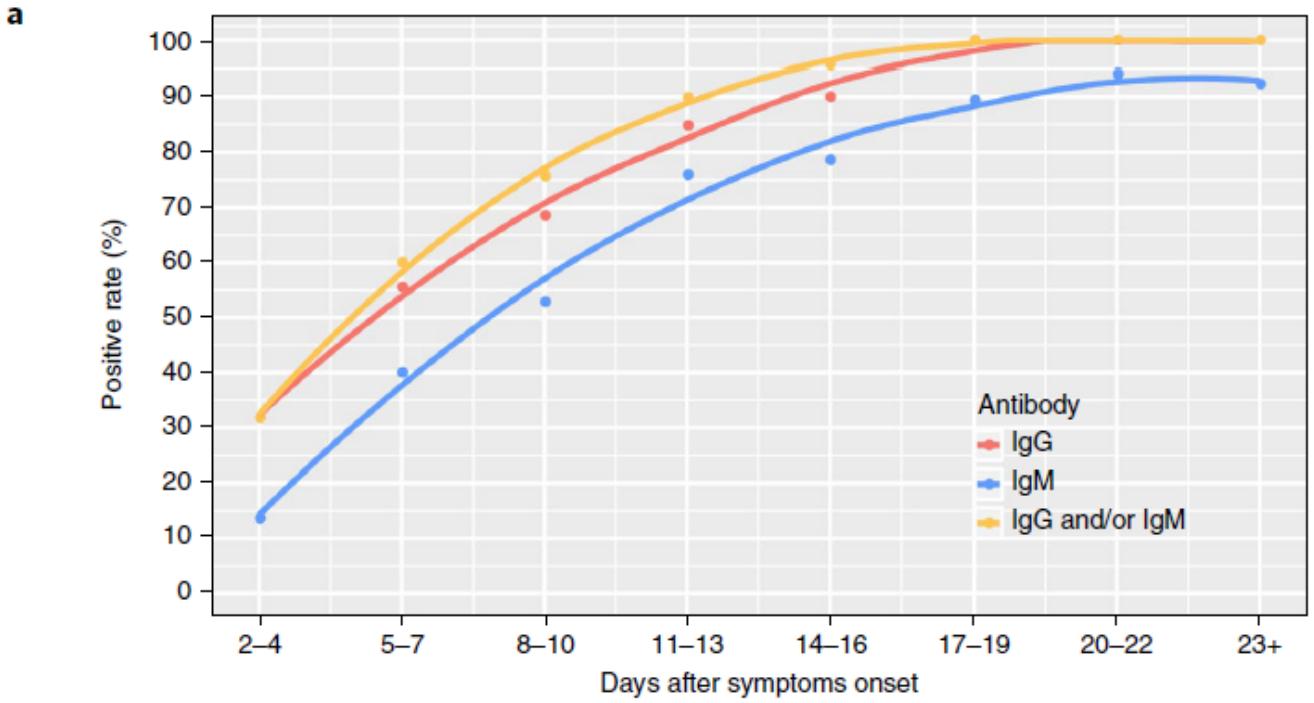
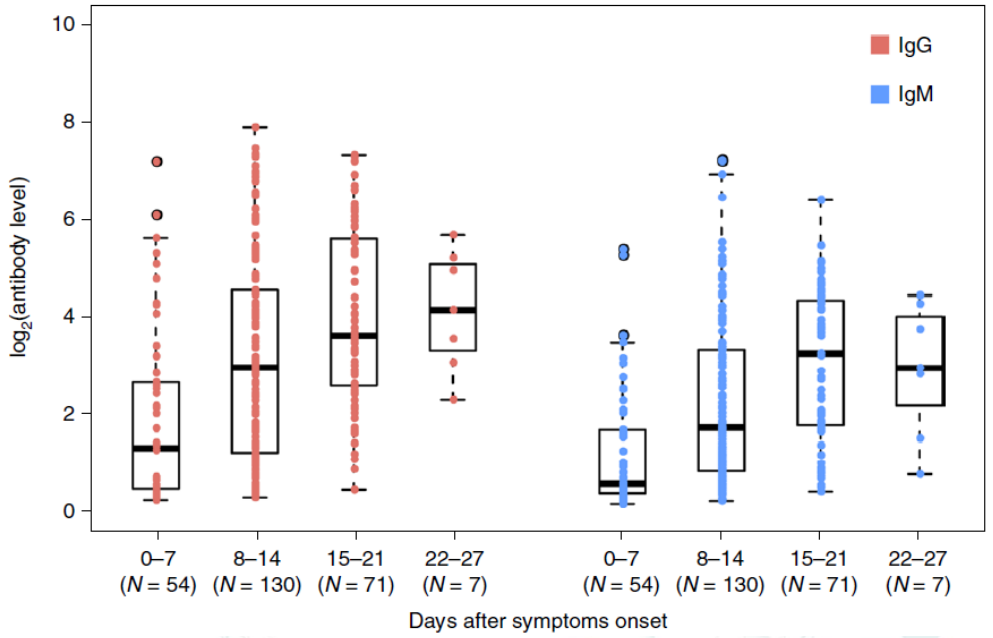
Ab responses in COVID19



Days *	2–4 (*N* = 22)	5–7 (*N* = 45)	8–10 (*N* = 70)	11–13 (*N* = 79)	14–16 (*N* = 70)	17–19 (*N* = 47)	20–22 (*N* = 17)	23+ (*N* = 13)
IgG	7	25	48	67	63	47	17	13
IgM	3	18	37	60	55	42	16	12
IgG and/or IgM	7	27	53	71	67	47	17	13



- 100% for IgG within 19d of onset of symptoms
- Seroconversion of IgM and IgG occurred simultaneously or sequentially
- Titers plateaued within 6d of seroconversion

Long et al. 2020
Nature Med

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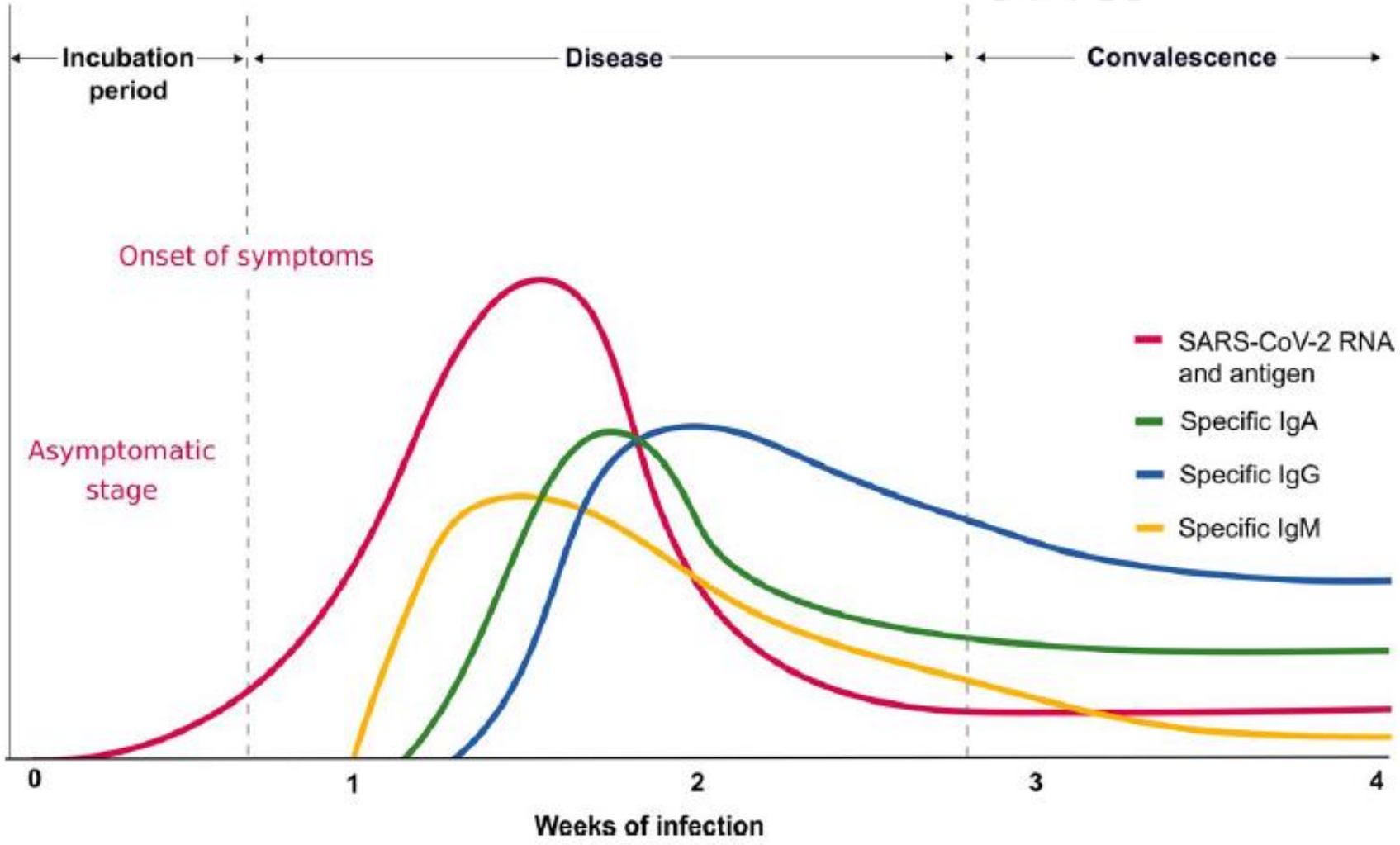
SARS CoV2 and Ab response



Azkur et al. 2020
Allergy

Take Home Points

- Viral shedding occurs prior to onset of symptoms
- Detection of replication competent virus declines with onset with most specimens without replication competent virus by d15 from onset
- Detection of antibodies dependent on timing of specimen collection:
  - Low likelihood of detecting antibodies within 7 days of symptom onset
  - Nearly 100% of cases with detectable Abs after day 15 from symptom onset

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Panel Discussion

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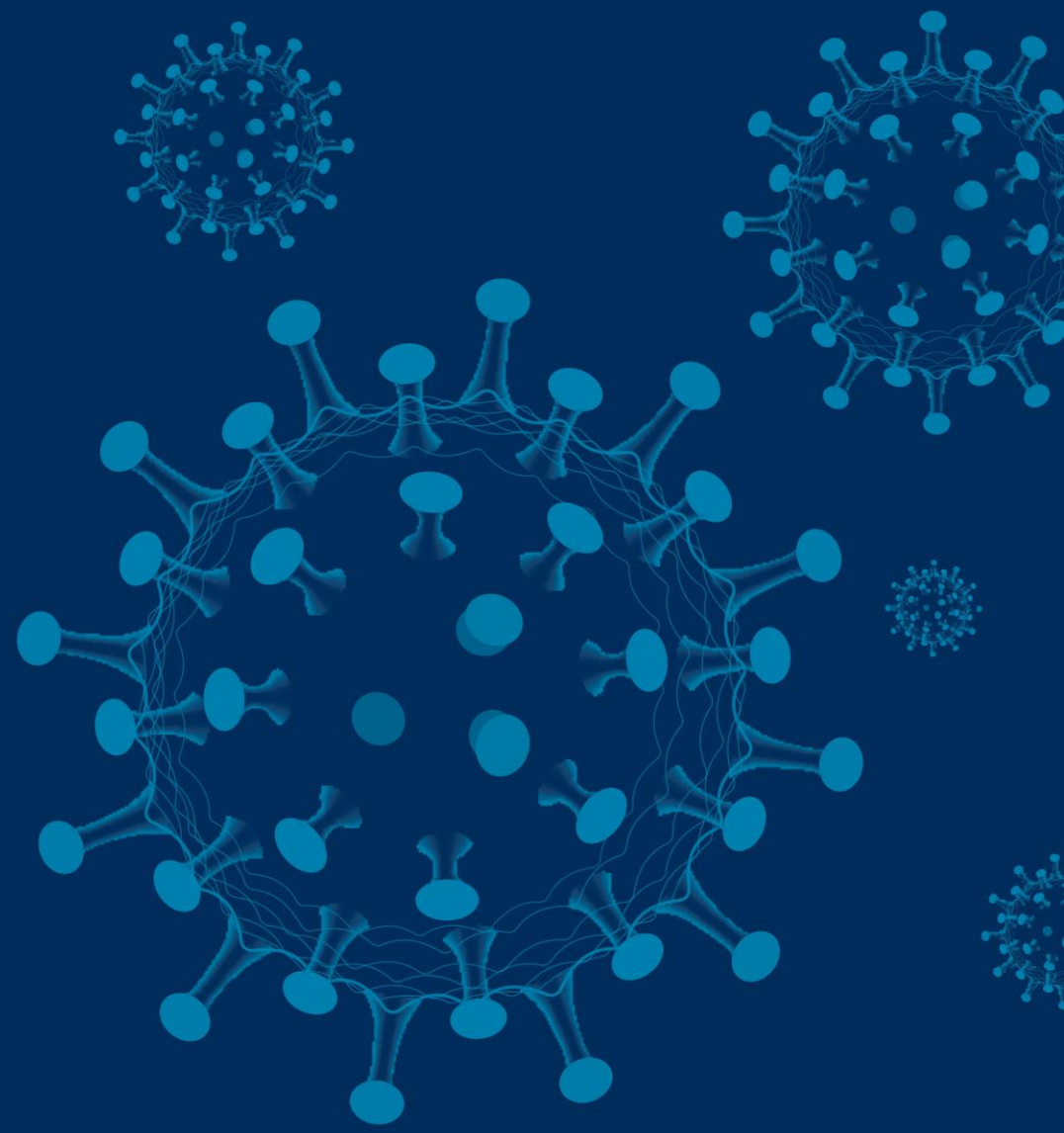
Testing

Dr. Steven Woloshin section



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The Promise and Pitfalls of Antibody Testing for SARS-CoV-2

Emily P. Hyle, MD MSc
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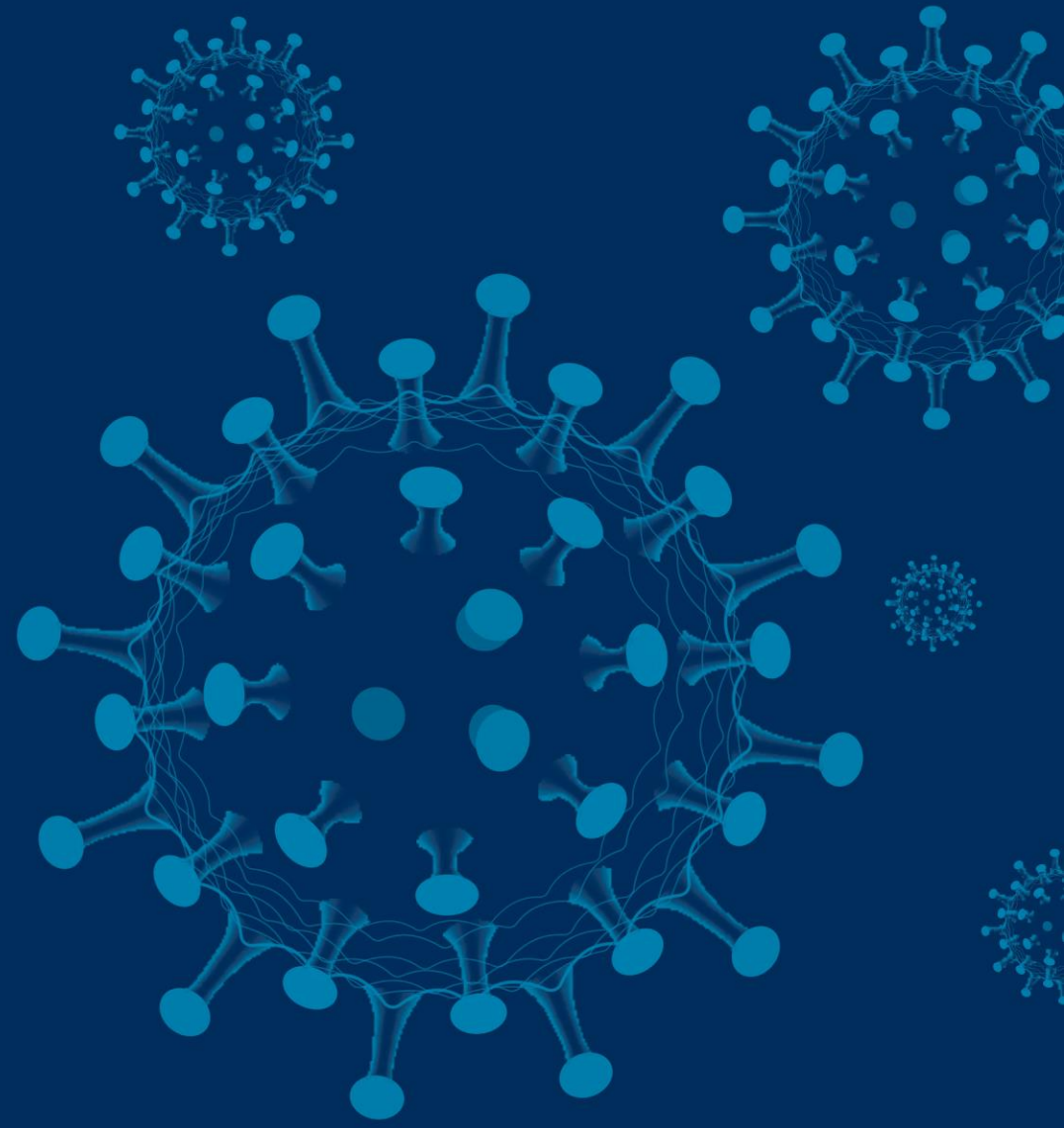

Key Takeaways

- Antibody testing can have a limited role in diagnosis of COVID-19 but should be used with caution
- More data are needed regarding whether detectable antibodies confer immunity to SARS-CoV-2
- Risks of false positive and false negative antibody tests remain unacceptably high for clinical decision-making when seroprevalence is low

Outline

- Antibodies for diagnosis
  - As a marker of recent or past infection
- Antibodies to identify immunity
  - As evidence to change clinical recommendations
- Antibody test characteristics
  - Sensitivity, specificity, population seroprevalence, R_0

Introduction

- SARS-CoV-2 has prompted an unprecedented era of innovation and scale-up of a variety of diagnostic tests
- Accurate and timely diagnosis of COVID-19 is essential to ensure appropriate isolation for patients and targeted use of personal protective equipment for staff and providers
- Antibodies are another tool in the armamentarium; they show promise but have pitfalls

Antibodies for diagnosis

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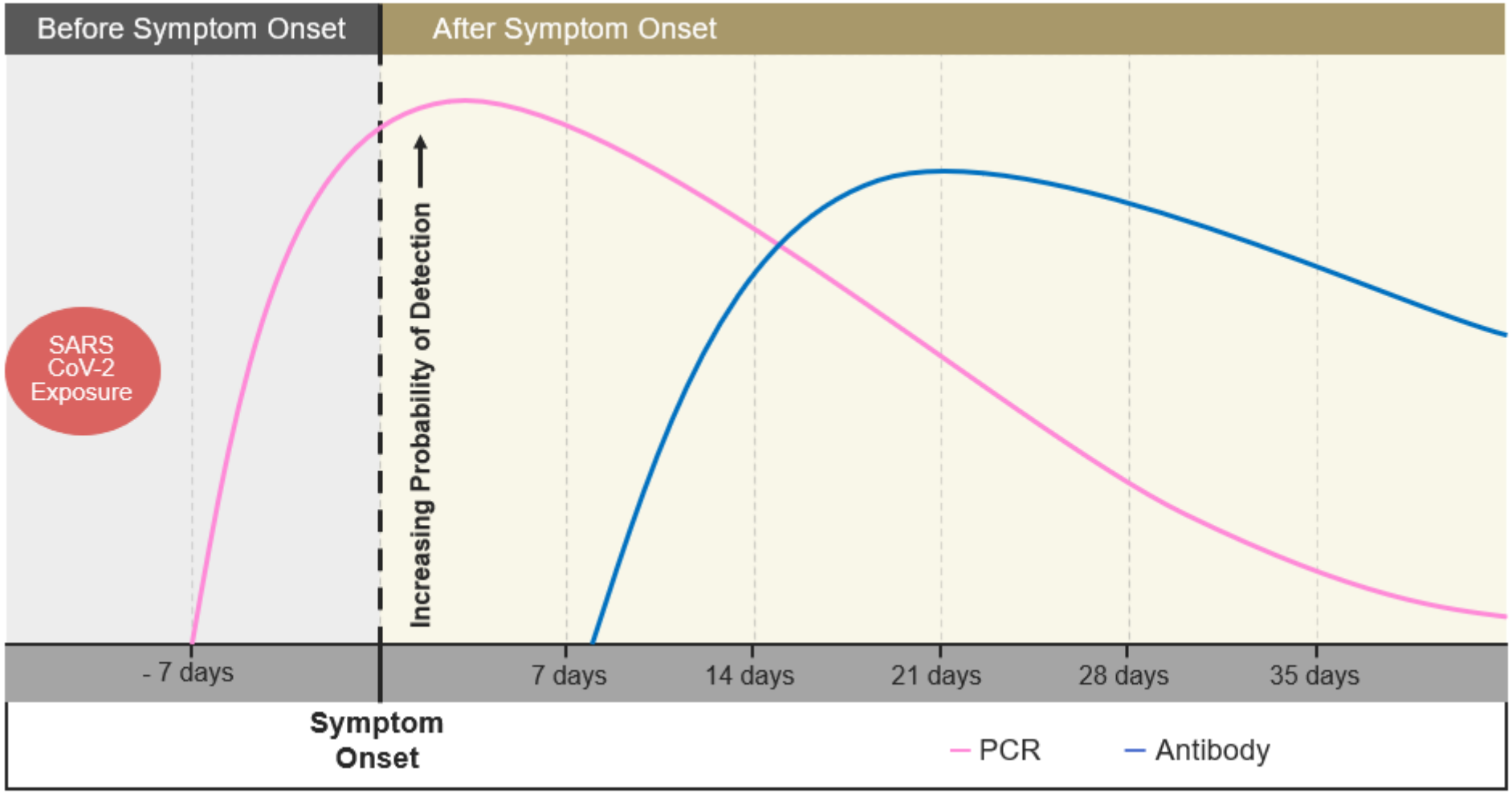


Adapted from Sethuraman et al. JAMA. 2020.

Antibodies for diagnosis

- Acute COVID-19:
  - Never useful early in illness
  - If antibody-positive after at least 8d of illness, can suggest COVID-19
  - If antibody-negative, cannot rule out COVID-19

- Past COVID-19:
  - Cross-reactivity with other coronaviruses appears to be low
  - Older or immunosuppressed less likely to make detectable antibodies
  - Data available for only 35 days after infection; long-term duration and significance of detectable antibodies remains unknown

Deeks et al. Cochrane Review. 2020.

Antibodies and immunity

Do positive antibodies = immunity?

- **We don't know for certain**
  - Based on other viral diseases, the presence of antibodies likely signals immunity to reinfection

- Many remaining questions
  - Does a certain level of antibodies need to be attained ("titer")?
  - If immune, how long will immunity persist? And can positive antibodies serve as a proxy for immunity over time?
  - If mild disease, will antibodies and immunity wane more rapidly?

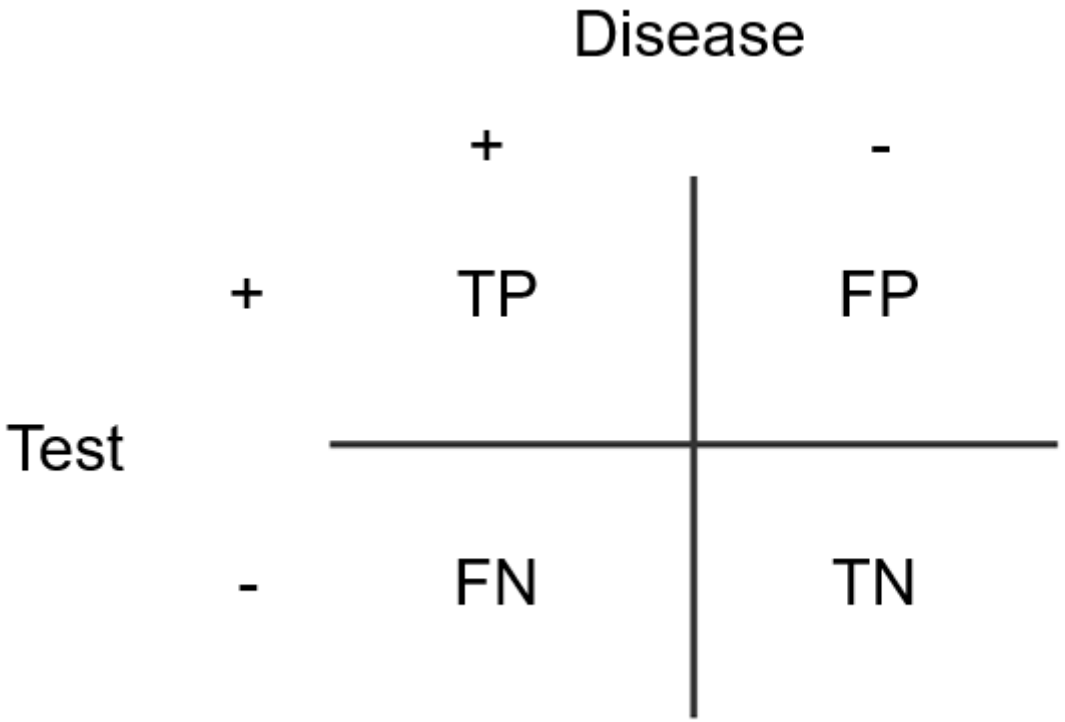
Ibarrondo et al. NEJM. 2020. Long et al. Nat Med. 2020.

Why do we want to know about immunity?

- Safely reduce adherence to social distancing guidelines
  - Wear masks?
  - Travel?
  - Attend in person work?
  - Visit vulnerable family and friends?
- Implications for “immune patients” in healthcare settings
  - Reduce COVID-19 testing?
  - Conserve PPE?
- Consequences are serious for false positive test results

Antibody test characteristics

Test characteristics: the 2x2 table



If +antibodies, will the patient have a + test?

		SARS-CoV-2 Antibodies +	SARS-CoV-2 Antibodies -
Test	+	TP	FP
	-	FN	TN
		Sensitivity	

Without antibodies, will the patient have a - test?

		SARS-CoV-2 Antibodies +	SARS-CoV-2 Antibodies -
Test	+	TP	FP
	-	FN	TN

Specificity

Current challenges with antibody tests

- A wide range of reported sensitivity and specificity
- Tested mostly among COVID-19 patients confirmed by RT-PCR
- Insufficient testing among non-hospitalized COVID-19 patients (ie, people with less severe disease or who are asymptomatic)

Deeks et al. Cochrane Review. 2020.

If test+, does the patient have antibodies?

	SARS-CoV-2 Antibodies +	SARS-CoV-2 Antibodies -	
Test +	TP	FP	**Positive Predictive Value**
Test -	FN	TN	

If test-, does the patient have no antibodies?

	SARS-CoV-2 Antibodies +	SARS-CoV-2 Antibodies -	
Test +	TP	FP	
Test -	FN	TN	**Negative Predictive Value**

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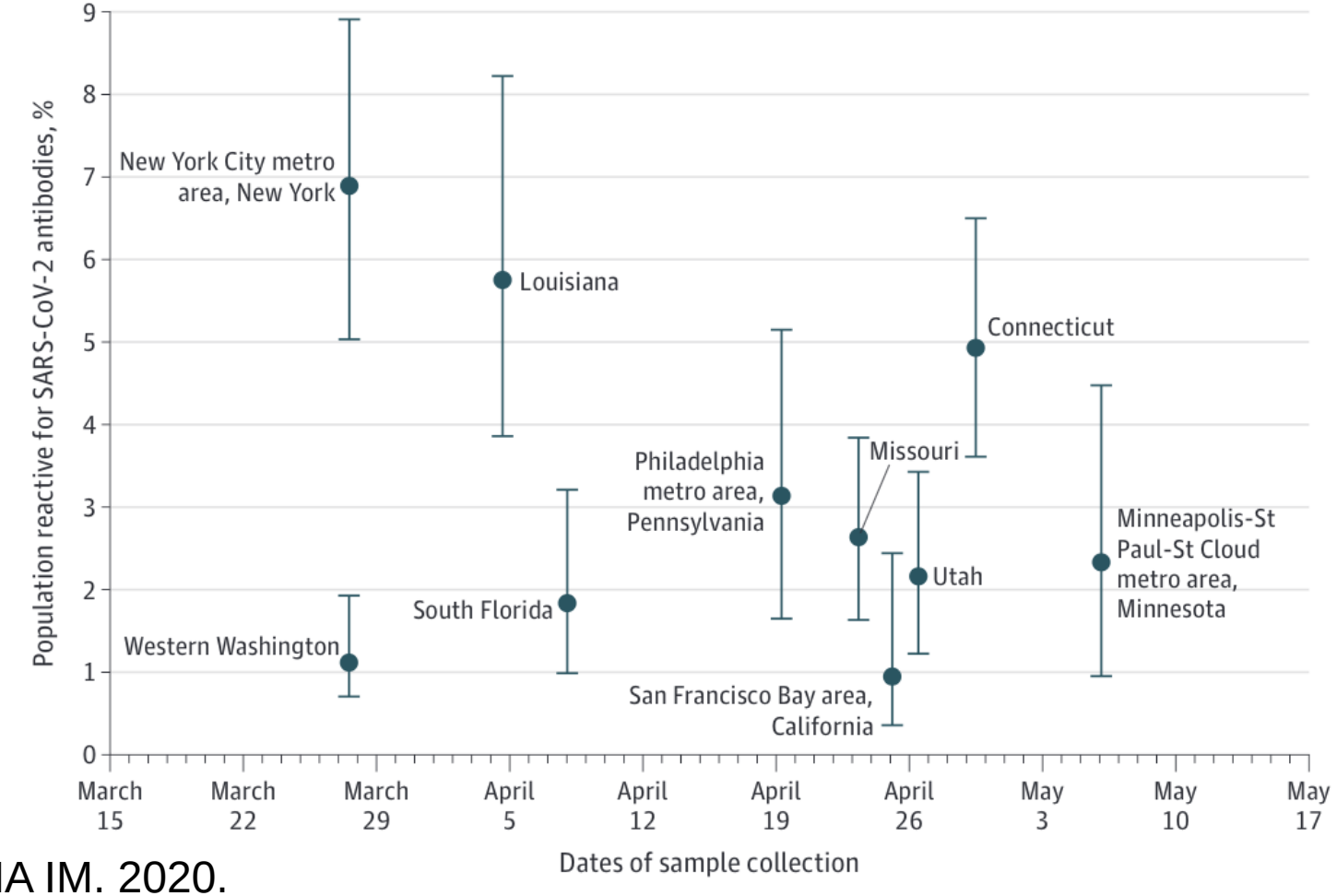
Seroprevalence remains low in the US



Havers et al. JAMA IM. 2020.

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If seroprevalence is 5%, then

True positive
False negative
False positive
True negative

Se: 92%
Sp: 98%

Deeks et al. Cochrane Review. 2020.

Perfect tests do not exist

- We use imperfect tests all the time in health care
  - Rapid flu tests (sensitivity: 50-70%; specificity: >90%)
  - BNP (sensitivity: >95%; specificity: >98%)

- Let's not wait for a "perfect" antibody test but rather think critically about the criteria at which the test would be useful
  - Specificity and sensitivity
  - Population seroprevalence
  - R_0 – the average number of transmissions resulting from one infection

Weinstein et al. NEJM. 2020; Wittemore et al, Clinical Infectious Diseases. 2020.

Key Takeaways

- Antibody testing can have a limited role in diagnosis of COVID-19 but should be used with caution
- More data are needed regarding whether detectable antibodies confer immunity to SARS-CoV-2
- Risks of false positive and false negative antibody tests remain unacceptably high for clinical decision-making when seroprevalence is low

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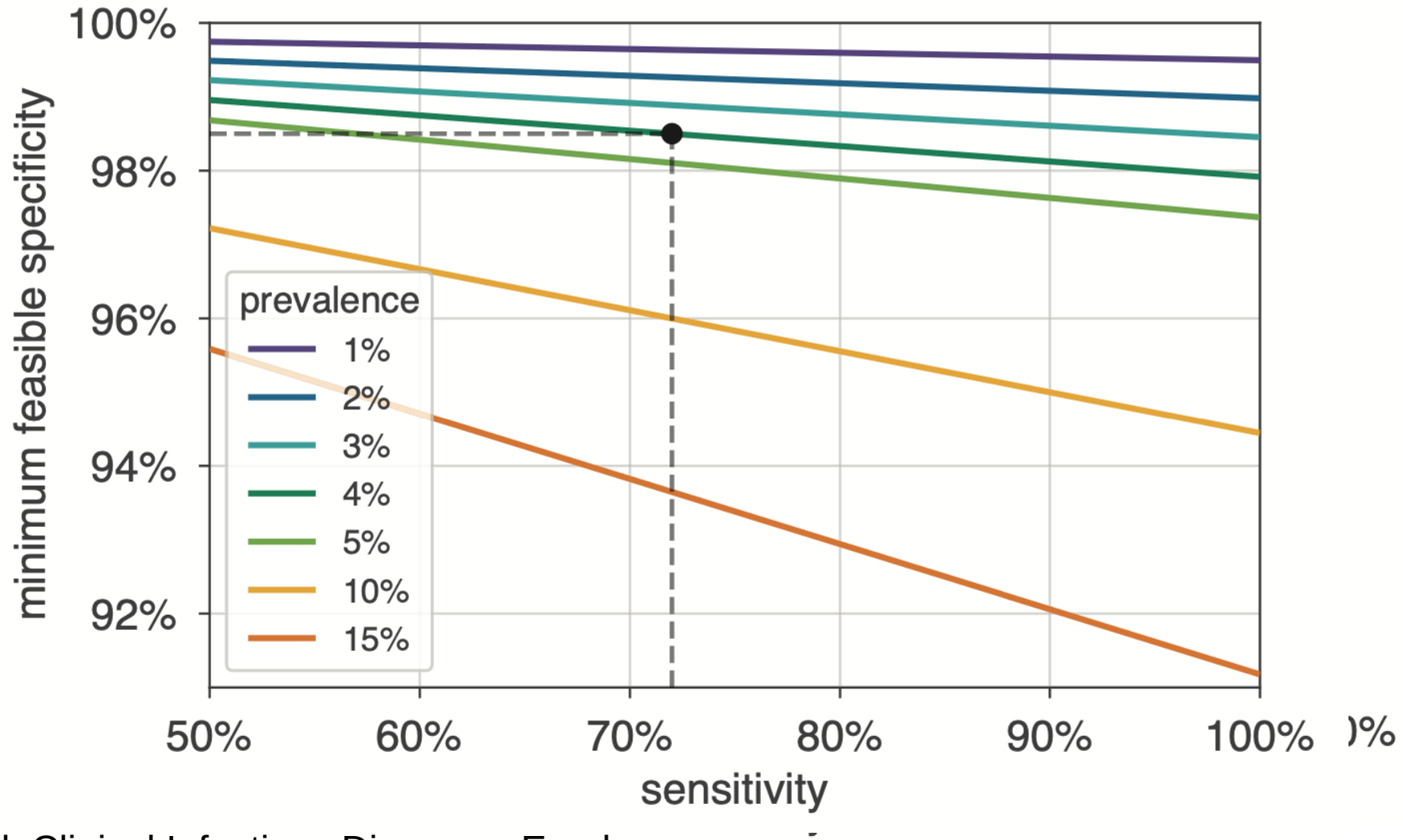
If seroprevalence is 20%, then

True positive
False negative
False positive
True negative

Se: 92%
Sp: 98%

Deeks et al. Cochrane Review. 2020.



Wittemore et al, Clinical Infectious Diseases. E-pub.

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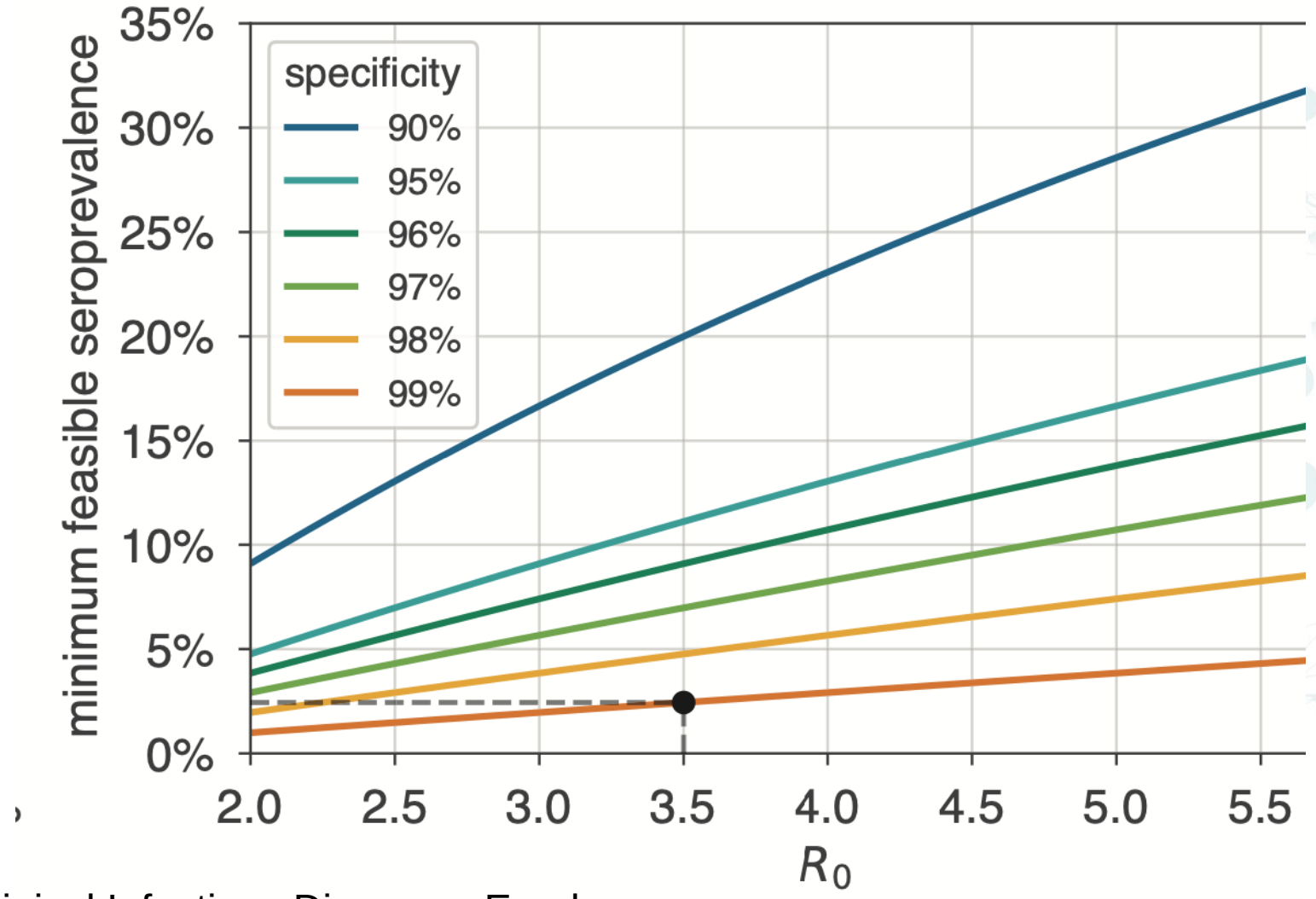

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