

COVID-19 Antibody Tests

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- This presentation is based on the information currently available. Recommendations may change as we gain more knowledge.
- **Most of the reports on this topic are anecdotal or “pre-print” and have not been reviewed by experts in the field.**

Overview

- Immunology 101 – antibodies review
- Types of antibody tests
- Biostatistics 101 – *this is REALLY important*
- Antibody tests in the United States
- Antibody surveillance testing in specific areas

Why are we interested in antibody testing?

- COVID-19 has no or mild symptoms in a large majority of people who have it
- Might only feel “a little sick” or not sick at all
- There might be a lot of people who have had the infection and recovered and don't know it.

Why are we interested in antibody testing?

- Those people should have some degree of immunity to the virus
 - We don't know how much
 - We don't know for how long
- People with immunity can be more active in the community
- More people with immunity slows the spread of the virus
- Helps decrease need for stay-at-home orders

Quick detour to talk about
masks

My mask protects you. Your mask protects me.

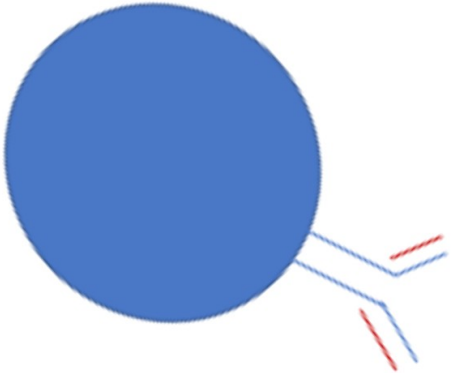
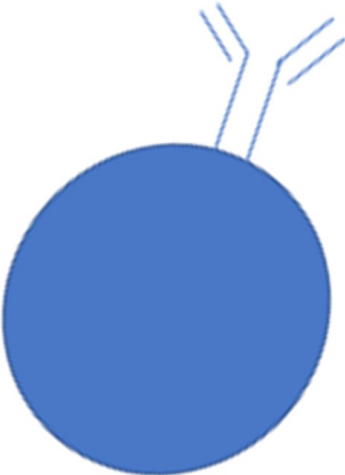
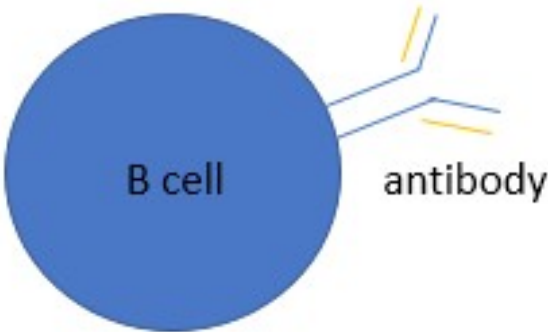
- COVID-19 has no or very mild symptoms in the majority of people who have it
- Even people who have more severe disease can spread the virus before they start to feel sick
- Wearing masks helps stop people who have the virus but feel well from unknowingly spreading it
- It's really about being a good neighbor

Immunology 101 - Antibody basics

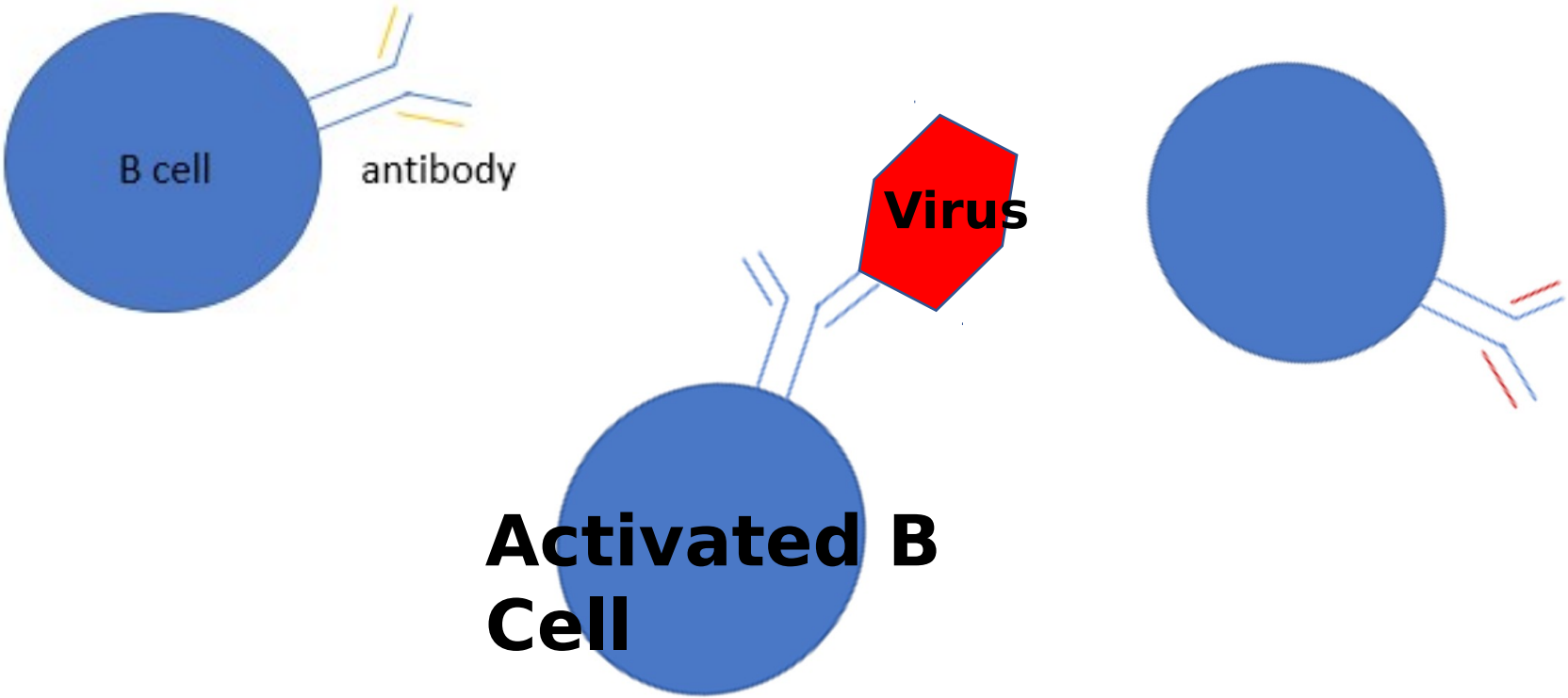
Immunology 101 - Antibody basics

- Antibody – protein made by your immune system that attaches to foreign proteins to remove them
- Billions of different antibodies attached to “B Cell” immune cells
- B Cell encounters a shape that doesn't belong in the body, attaches to it

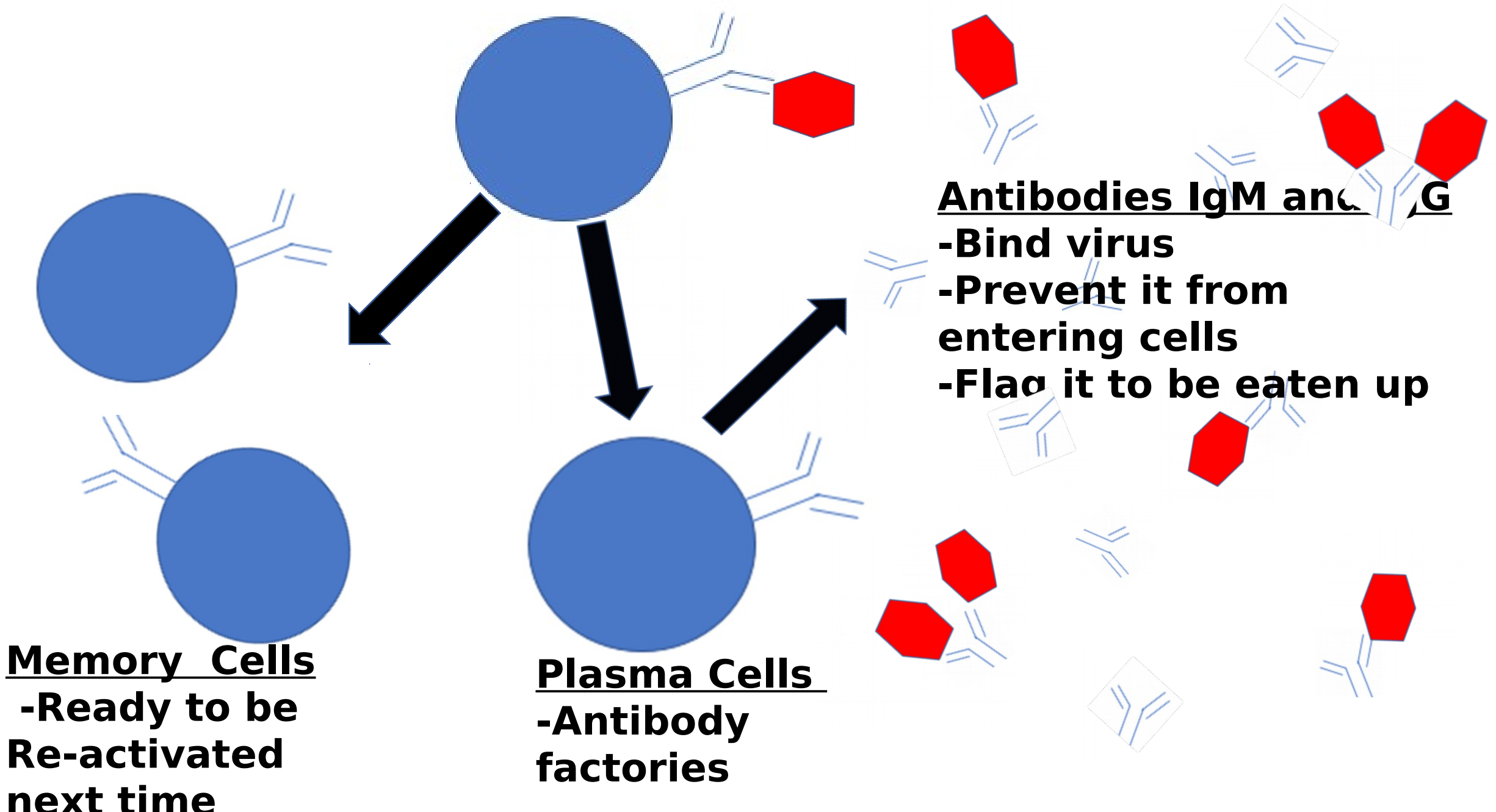
Antibody basics



Antibody basics



Activated B Cell



Types of Antibody Tests


Types of Antibody Tests

Type of test	Pros	Cons	What it cannot tell us
Rapid diagnostic test (RDT) "Home test"	Simple Fast (10-30 min)	May not be as accurate	The amount of antibodies, or if these antibodies are able to inhibit virus growth
Enzyme linked immunosorbent assay (ELISA)	More accurate Determines amount of antibodies 3-5 hrs	Requires more lab resources	If the antibodies are able to inhibit virus growth.
Chemiluminescent immunoassay	More accurate Determines amount of antibodies	Requires more lab resources.	If the antibodies are able to inhibit virus growth.

Biostatistics 101

The test isn't always right

Biostatistics 101 - Definitions

- You have a disease
- False negative -you have the disease, but the test is negative
- $100 - \text{false negative rate} = \text{“Sensitivity”}$ of the test
- A test that has 0 false negative results is “100% sensitive” for the disease
- A test that has 10% false negatives is “90% sensitive” for the disease
-  Sensitivity = False negative

Biostatistics 101 - Definitions

- You don't have a disease
- False positive – you DON'T have the disease, but the test is positive
- $100 - \text{False positive rate} = \text{“Specificity”}$ of the test
- A test that has 0 false positive results is “100% specific” for a disease
- A test that has 5% false positives is “95% specific” for a disease
- $\text{Specificity} = 1 - \frac{\text{False positives}}{\text{Total without disease}}$

False positives – why does it matter

- You are giving people false sense of safety when they are still at risk
- If people then DO get sick, it creates a false narrative of people getting sick again after recovering
- Overestimates the immunity in the population and underestimates further spread of the virus

False positives – why does it matter

- The problem is magnified when it is early the outbreak and not a lot of people have the disease
- And yes, it's still early in the outbreak, and not a lot of people have the disease

A Problem to Show The
Problem with False
Positives

The Problem with False positives

- HYPOTHETICAL EXAMPLE
- Santa Fe County population 150,000
- 100 people in the county were diagnosed with the disease
- 5,000 other people in the county have had the disease but were not tested because they didn't feel sick

False positives – hypothetical example

- Let's do antibody testing on 1% of the residents who were not sick get an idea of how many people might have already recovered!
 - 1500 people
 - 50 had disease
 - 1450 did not have disease
- The test has **10% false positives = 90% specific**
- The test has 2% false negatives = 98% sensitive

False positives – IS 10% GOOD ENOUGH?

	Had Disease 50 people	No Disease 1450 people	Total Tested 1500 people	
Test Positive	49	145	194 positive tests	$145/194 =$ <u>75% of positive tests DIDN'T HAVE DISEASE!!!</u>
Test Negative	1	1305	1306 negative tests	$1305/1306 =$ 99.9% negative

False positives – IS 10% GOOD ENOUGH?

- $145/194 = 75\%$ of people who test positive did not have disease!
- Health officials see $194/1500 = 13\%$ of the survey group have had it
- NO!!
- $50/1500 = 3\%$ have had it
- Is 90% specific good enough?

False positives – IS 2% GOOD ENOUGH?

	Had Disease 50 people	No Disease 1450 people		
Test Positive	49	29	78 positive tests	$29/78 =$ <u>37% of positive tests DIDN'T HAVE DISEASE!!!</u>
Test Negative	1	1421	1422 negative tests	$1421/1422 = 99.9\%$ negative tests didn't

False positives – IS 2% GOOD ENOUGH?

- $29/78 = 37\%$ of people who test positive did not have disease!
- Health officials see $78/1500 = 5\%$ of the survey group have had it
- NO!!
- $50/1700 = 3\%$ have had it
- 98% Specific is a whole lot better

In My Opinion...

- 10% false positives (90% specific) isn't good enough
- I'll settle for 98% specific
- WE NEED TO GET THIS RIGHT

FDA policy

<https://www.fda.gov/news-events/fda-voices/insight-fdas-revised-policy-antibody-tests-prioritizing-access-and-accuracy>

<https://www.fda.gov/media/135659/download>

FDA Policy

- Updated May 4, 2020
- Time limit for manufacturers to submit data to FDA
- Defines thresholds for performance of tests (false positives/negatives)
- Requires manufacturers to alert consumers about possibility of false results and steps to address this.

Status of tests in USA

<https://www.centerforhealthsecurity.org/resources/COVID-19/serology/Serology-based-tests-for-COVID-19.html#sec4>

May 1, 2020

- 7 FDA approved tests
- 34 approved tests for research and surveillance
- 15 tests in development
- More than ½ the manufacturers have not provided their false positive and false negative rates
- False positive rates vary from 0 to 10%

Direct to Consumer Antibody Testing

- Quest diagnostics
- Online screening questions
- Go to a lab for blood draw
- \$119
- Results posted securely online
- What's the specificity? How many false positive tests?
- ?????

Direct to Consumer Antibody Testing

- Quest diagnostics
- “The IgG antibody serology test has not been reviewed by the FDA.”
- “Results from antibody testing should not be used as the sole basis to diagnose or exclude SARS-CoV-2 infection or to inform infection status.”
- “Positive results may be due to past or present infection with non-SARS-CoV-2 coronavirus strains, such as coronavirus HKU1, NL63, OC43, or 229E”

<https://www.questdiagnostics.com/home/Covid-19/Patients>

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Phrases to look for

- “Specificity” --- ideally 98% or higher
- “Negative percent agreement” – ideally 98% or higher
- “False positive
- *“not to be used as a sole basis for diagnosis”* – taking the manufacturer’s word for it...BUYER BEWARE
- “Positive results may be due to...” -- alerts you to false positives

Antibody Surveillance Testing

Antibody Surveillance Testing

- New York City – 21% (Specificity?? = false positive rate ??)
- Southern California – 4.1% (99.5% specific = 0.5% false positives)
- Northern California – 1.2 – 2.8% (Same test as above)
- Chelsea (Boston) – 31.5% (90% specific = 10% false positives ouch!)

- Robbio, Italy – 10% (??)
- Gangelt, Germany – 14% (??)

The Bottom Line

- Antibody surveillance testing in areas of COVID-19 outbreaks suggest 1 – 30% of people may have already been infected and recovered
- At this stage, “false positive” test results can dramatically mislead individuals and policy makers
- A lot of Direct-to-Consumer antibody tests will be marketed in the coming months.
- Because of the emergency, tests are not being held to the usual FDA standards to ensure they are valid – it is up to the manufacturer
- WE SHOULD INSIST ON THE MOST SPECIFIC TESTS POSSIBLE

Thank you!

- Amanda Lewis Janet Phillips Greg Shores Brittney VanDerWerff



ge watch all the presentations here!

jsplibrary.org

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References

- 1) Bendavid, E et.al., *COVID-19 Antibody Seroprevalence in Santa Clara County, California* [pre-print doi: 10.1101/2020.04.14.2006246](https://doi.org/10.1101/2020.04.14.2006246)
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