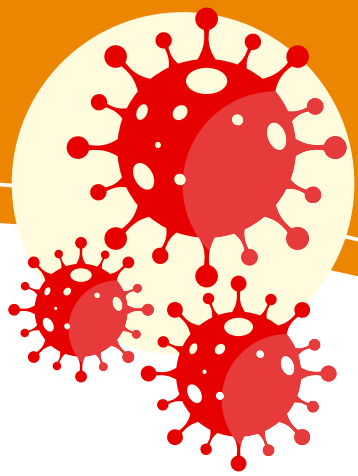
Testing for coronavirus

A WMUK factsheet

produced by Dr Shirley D'Sa, WMUK trustee
and lead WM clinician at UCLH



The basics

When we encounter any sort of infection, our immune systems respond quickly with the objective of overcoming the infection and generating memory against the infectious agent so as to protect us from getting it again in the future (immunity).

The outcome of the immune response depends on many factors:

Individual	External	Viral
• Age • General fitness • Health of the immune system – White blood cells – Immunoglobulin (antibody levels) – Autoimmune problems • Specific vulnerabilities (such as lung disease)	• Previous and current immunosuppressive treatments • Living conditions- proximity to others (as carriers of the virus) • Diet? • Stressors?	• The virulence (potency) of the virus • The way the virus enters the body- preferentially triggers different aspects of the immune system • Previous exposure to similar viruses (this might 'prime' the immune system to some extent)

The impact of the above factors is not predictable in individuals; although a few measurements can be made (such as white cell count and normal antibody levels, lung function tests etc.), the sum of the parts may be greater than the whole. Therefore, doctors make an estimate of likely risk and advise accordingly. Since the onset of the pandemic, the tendency has been to exercise caution and err on the side of safety until we have more evidence on which to base guidance.

Antibody production in response to an infection

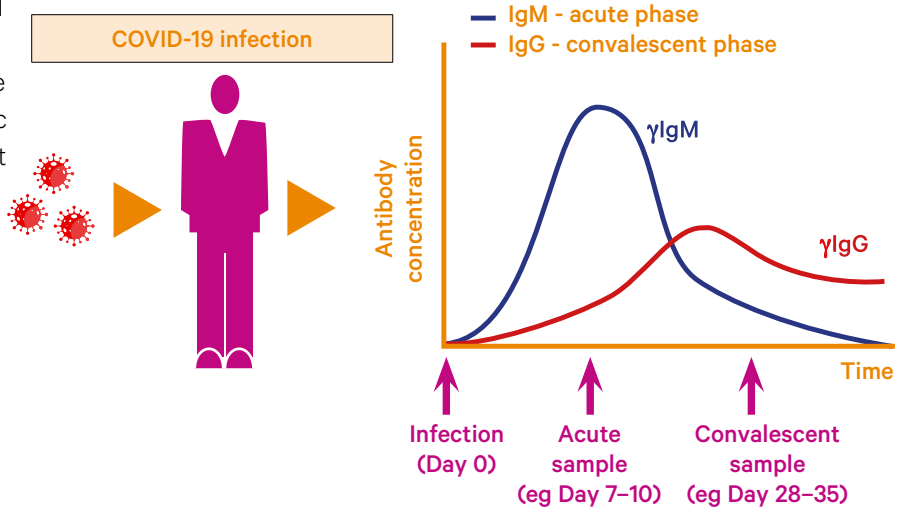
Antibodies are produced by our B lymphocytes and plasma cells. As WM patients, you may be familiar with these cells, as Waldenstrom's disease comprises exactly these types of cells!

Indeed, WM is the result of accumulation of these immune type cells, but they are not immunologically useful. In fact, they are faulty cells whose accumulation results in the manifestations of WM, which often includes under-functioning of the normal immune system, as it gets side-tracked into the growth of the diseased cells.

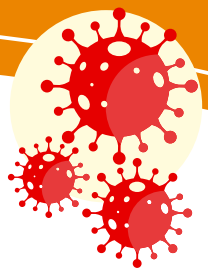
Irrespective of the WM, there are normal immune cells present which try to respond to infections when they arise. In doing so, the first kind of antibody (directed against the infection) produced within a timescale of 7 to 10 days is **IgM**.

This antibody is only produced temporarily and then disappears. Notably, this is different to the monoclonal IgM produced by the WM cells (the paraprotein or M-protein). Rather, it is a specific IgM produced by normal immune cells to target the infection as part of the immune response. Testing for this specific IgM is not affected by the presence of the monoclonal IgM, whatever the level.

Also produced but at a slower rate is **IgG**, peaking at 4 to 6 weeks but remaining detectable in the blood stream long-term, at a low level to provide lasting immunity to the infection.



Testing for coronavirus



What is known about the immune response to COVID-19?

COVID-19 is the name given to the disease caused by the novel SARS-CoV-2 virus that has reached pandemic proportions since its discovery in China, in November 2019. It is a type of coronavirus – of which many strains already exist, resulting in generally mild respiratory tract infections including the common cold.

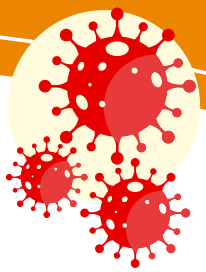
Previous more serious coronavirus outbreaks in so called zoonotic viruses (those that cross from animals to humans) include SARS-CoV and MERS, which caused outbreaks in China and the Middle East respectively. For incompletely understood reasons, those outbreaks were contained and did not reach the rest of the globe.

As COVID-19 is a new infection in humans, we are still gaining information about its behaviour as it infects humans as well as how the human immune system responds (with all the caveats in the table below).

The immune response clearly varies with some persons being asymptomatic while others experiencing a so-called 'cytokine storm' which is a vigorous immune reaction to the virus resulting in severe infection, sometimes resulting in death.

Testing is key, but how and when?

Type of test	Molecular test	Antibody test	Antigen test
What is it?	Molecular tests detect genetic material (RNA) from the virus at the site of infection (the respiratory tract).	This test detects the antibodies produced in response to the infection (IgM or IgG).	The newest of all tests, which detects pieces of the virus that are recognised by the immune system.
Sample needed	A nose or throat swab	Blood sample	Nose swab
What is detected?	A series of chemical reactions (known as PCR) copies **viral RNA** if present at the site of the swab.	A well tested method is used to detect whether **antibodies against COVID-19** are present in the blood stream.	Antibodies are used to detect **viral antigens** in the laboratory.
What does the result mean?	It means that you are infected at the time of the test and have viral material in your respiratory tract (and therefore potentially infectious to others).	Whether you were infected in the past	Evidence for a current infection and potentially infectious to others
How does the result help?	If you have a positive swab result, you should be isolated from others and your contacts should also be tested (ideally) [CONTACT TRACING].	It identifies people who may have immunity and whose antibodies could be used to treat COVID-19 patients. However the sensitivity and specificity of these tests (number of true positives and true negatives) needs optimisation.	Same information as the molecular test: whether you are currently infected and should be isolated from others.
Limitations of the test	A negative test may be due to 3 reasons: • Not enough material was captured by the swab [FALSE NEGATIVE] – this may result in infected people remaining a risk to others. • You have not been infected • You were infected but are no longer carrying the virus. FALSE POSITIVE results (positive test but never infected) may occur due to misreading of the viral RNA, which may bear similarities to other Coronaviruses. This may result in unnecessary quarantine.	A positive test does not mean you are immune to the virus. It is unclear if antibodies provide protection, provide long-term immunity or what level of antibody response is protective. Many antibody tests are being manufactured - many were given emergency FDA approval before they were independently validated. A negative test does not definitely mean that you did not have COVID-19. Some people with WM may have low antibody levels and so cannot mount a response to the infection.	A negative result does not mean that you are immune to the virus. The antigen test is not as accurate as molecular tests. It is still in development and any available kits which may become available via internet purchase should be viewed with caution. Please discuss with your doctor before using such a test.
What is next?	There is emerging evidence that saliva samples may provide a reliable source and be more easily obtainable and less uncomfortable to acquire.	Ongoing efforts are underway to produce reliable and sensitive tests. Once there is a reliable test, rapid upscaling of the test will be needed to enable widespread use.	Could provide a result in 15 minutes using a kit - no need for a laboratory.



Are antibodies against COVID-19 protective?

We do not know this yet. Not everyone who contracts the virus develops antibodies, but many still recover from the infection. It is not known whether antibodies that are currently detectable by the available methods are 'neutralising' – in other words- whether they provide protection against the virus in the future.

At present, the various tests in circulation comprise one of the methods described above - the policies regarding who and when to test are evolving daily and vary from region to region as there is no consensus yet as to who should be tested and how. Within the next 4 to 6 weeks, as more data are gathered from test results in different clinical situations, more information will become available.

Some people with WM will have low antibody levels in general (hypogammaglobulinaemia) and so may not generate antibodies specifically to COVID-19 should they be exposed to it. Some of these patients may be on regular immunoglobulin infusions to reduce the number of infections they have but there is no evidence at present that this is protective against COVID-19 although there are some trials investigating this currently.

Conclusion

There remain many uncertainties around testing for COVID-19. The field is rapidly developing but caution is needed in interpreting results and what they mean in practical terms. It is important to seek the advice of your medical team regarding testing. Not all tests are available to patients as they are still in development.

At present, we advise ongoing caution regarding shielding measures.

Remember **PREVENTION IS BETTER THAN NO CURE!**

Publication date: September 2020
Review date: September 2022

Reference

False Negative Tests for SARS-CoV-2 Infection – Challenges and Implications. Woloshin *et al. New England Journal of Medicine* June 2020

Acknowledgements

Professor Anna Schuh, Director of Molecular Diagnostics, Department of Oncology, University of Oxford, and

Dr Dima El-Sharkawi, WMUK trustee and Consultant Haematologist at the Royal Marsden Hospital, London, for sharing their invaluable insights on this topic.