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What is the diagnostic accuracy of antibody tests for the detection of infection with the COVID-19 virus?

Plasma from people who have recovered from COVID-19 to treat individuals with COVID-19

How accurate are rapid tests, performed during a health-care visit (point-of-care), for diagnosing COVID-19?

What is the diagnostic accuracy of antibody tests for the detection of infection with the COVID-19 virus?

Authors: Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Spijker R, Taylor-Phillips S, Adriano A, Beese S, Dretzke J, Ferrante di Ruffano L, Harris IM, Price MJ, Dittrich S, Emperador D, Hooft L, Leeflang MMG, Van den Bruel A

Background

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus that spreads easily between people in a similar way to the common cold or 'flu. Most people with COVID-19 have a mild to moderate respiratory illness, and some may have no symptoms (asymptomatic infection). Others experience severe symptoms and need specialist treatment and intensive care.

The immune system of people who have COVID-19 responds to infection by developing proteins that can attack the virus (antibodies) in their blood. Tests to detect antibodies in peoples' blood might show whether they currently have COVID-19 or have had it previously.

Why are accurate tests important?

Accurate testing allows identification of people who might need treatment, or who need to isolate themselves to prevent the spread of infection. Failure to detect people with COVID-19 when it is present (a false negative result) may delay treatment and risk further spread of infection to others. Incorrect identification of COVID-19 when it is not present (a false positive result) may lead to unnecessary further testing, treatment, and isolation of the person and close contacts. Correct identification of people who have previously had COVID-19 is important in measuring disease spread, assessing the success of public health interventions (like isolation), and potentially in identifying individuals with immunity (should antibodies in the future be shown to indicate immunity).

To identify false negative and false positive results, antibody test results are compared in people known to have COVID-19 and known not to have COVID-19. Study participants are classified as to whether they are known or not known to have COVID-19 based on criteria known as the 'reference standard'. Many studies use

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samples taken from the nose and throat to identify people with COVID-19. The samples undergo a test called reverse transcriptase polymerase chain reaction (RT-PCR). This testing process can sometimes miss infection (false negative result), but additional tests can identify COVID-19 infection in people with a negative RT-PCR result. These include measuring clinical symptoms, like coughing or high temperature, or 'imaging' tests like chest X-rays. People known not to have COVID-19 are sometimes identified from stored blood samples taken before COVID-19 existed, or from patients with respiratory symptoms found to be caused by other diseases.

What did the review study?

The studies looked at three types of antibody, IgA, IgG and IgM. Most tests measure both IgG and IgM, but some measure a single antibody or combinations of the three antibodies.

Levels of antibodies rise and fall at different times after infection. IgG is the last to rise but lasts longest. Levels of antibodies are usually highest a few weeks after infection.

Some antibody tests need specialist laboratory equipment. Others use disposable devices, similar to pregnancy tests. These tests can be used in laboratories or wherever the patient is (point-of-care), in hospital or at home.

We wanted to find out whether antibody tests:

- are accurate enough to diagnose infection in people with or without symptoms of COVID-19, and
- can be used to find out if someone has already had COVID-19.

What did we do?

We looked for studies that measured the accuracy of antibody tests compared with reference standard criteria to detect current or past COVID-19 infection. Studies could assess any antibody test compared with any reference standard. People could be tested in hospital or the community. Studies could test people known to have – or not to have – or be suspected of having COVID-19.

Study characteristics

We found 54 relevant studies. Studies took place in Asia (38), Europe (15), and in both USA and China (1).

Forty-six studies included people who were in hospital with suspected or confirmed COVID-19 infection only.

Twenty-nine studies compared test results in people with COVID-19 with test results in healthy people or people with other diseases.

Not all studies provided details about participants' age and gender. Often, we could not tell whether studies were evaluating current or past infection, as few reported whether participants were recovering. We did not find any studies that tested only asymptomatic people.

Main results

Our findings come mainly from 38 studies that provided results based on the time since people first noticed symptoms.

Antibody tests one week after first symptoms only detected 30% of people who had COVID-19. Accuracy increased in week 2 with 70% detected, and was highest in week 3 (more than 90% detected). Little evidence was available after week 3. Tests gave false positive results in 2% of those without COVID-19.

Results from IgG/IgM tests three weeks after symptoms started suggested that if 1000 people had antibody tests, and 50 (5%) of them really had COVID-19 (as we might expect in a national screening survey):

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- 58 people would test positive for COVID-19. Of these, 12 people (21%) would not have COVID-19 (false positive result).
- 942 people would test negative for COVID-19. Of these, 4 people (0.4%) would actually have COVID-19 (false negative result).

If we tested 1000 healthcare workers (in a high-risk setting) who had had symptoms, and 500 (50%) of them really had COVID-19:

- 464 people would test positive for COVID-19. Of these, 7 people (2%) would not have COVID-19 (false positive result).
- 537 people would test negative for COVID-19. Of these, 43 (8%) would actually have COVID-19 (false negative result).

We did not find convincing differences in accuracy for different types of antibody test.

How reliable were the results of the studies of this review?

Our confidence in the evidence is limited for several reasons. In general, studies were small, did not use the most reliable methods and did not report their results fully. Often, they did not include patients with COVID-19 who may have had a false negative result on PCR, and took their data for people without COVID-19 from records of tests done before COVID-19 arose. This may have affected test accuracy, but it is impossible to identify by how much.

Who do the results of this review apply to?

Most participants were in hospital with COVID-19, so were likely to have more severe disease than people with mild symptoms who were not hospitalised. This means that we don't know how accurate antibody tests are for people with milder disease or no symptoms.

More than half of the studies assessed tests they had developed themselves, most of which are not available to buy. Many studies were published quickly online as ‘preprints’. Preprints do not undergo the normal rigorous checks of published studies, so we are not certain how reliable they are.

As most studies took place in Asia, we don't know whether test results would be similar elsewhere in the world.

What are the implications of this review?

The review shows that antibody tests could have a useful role in detecting if someone has had COVID-19, but the timing of when the tests are used is important. Antibody tests may help to confirm COVID-19 infection in people who have had symptoms for more than two weeks and do not have a RT-PCR test, or have negative RT-PCR test results. The tests are better at detecting COVID-19 in people two or more weeks after their symptoms started, but we do not know how well they work more than five weeks after symptoms started. We do not know how well the tests work for people who have milder disease or no symptoms, because the studies in the review were mainly done in people who were in hospital. In time, we will learn whether having previously had COVID-19 provides individuals with immunity to future infection.

Further research is needed into the use of antibody tests in people recovering from COVID-19 infection, and in people who have experienced mild symptoms or who never experienced symptoms.

How up-to-date is this review?

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This review includes evidence published up to 27 April 2020. Because a lot of new research is being published in this field, we will update this review frequently.

Plasma from people who have recovered from COVID-19 to treat individuals with COVID-19

Authors: Piechotta V, Chai KL, Valk SJ, Doree C, Monsef I, Wood EM, Lamikanra A, Kimber C, McQuilten Z, So-Osman C, Estcourt LJ, Skoetz N

Coronavirus disease 2019 (COVID-19) is a highly infectious respiratory illness caused by a newly recognised type of coronavirus. People infected with this virus may not show signs of the disease, others may develop symptoms, including fever, cough, shortness of breath and sore throat. In some people the infection is more severe and can cause breathing difficulties, leading to hospitalisation, admission to intensive care or death. Currently, no vaccine or specific treatment is available.

People who have recovered from COVID-19 develop natural defences to the disease in their blood (antibodies). Antibodies are found in part of the blood called plasma. Plasma from blood donated from recovered patients, which contains COVID-19 antibodies, can be used to make two preparations. Firstly, convalescent plasma, which is plasma that contains these antibodies. Secondly, hyperimmune immunoglobulin, which is more concentrated, and therefore contains more antibodies.

Convalescent plasma and hyperimmune immunoglobulin have been used successfully to treat other respiratory viruses. These treatments (given by a drip or injection) are generally well-tolerated, but unwanted effects can occur.

What did we want to find?

We wanted to know whether plasma from people who have recovered from COVID-19 is an effective treatment for people with COVID-19, and whether this treatment causes any unwanted effects. We are continually updating this review as more evidence becomes available.

Our methods

On 4 June 2020 we searched major medical databases for clinical studies on treatment with convalescent plasma or hyperimmune immunoglobulin for people with COVID-19. Studies could be conducted anywhere in the world and include participants of any age, gender or ethnicity, with mild, moderate or severe COVID-19.

Key results

We included 20 completed studies with 5443 participants; 5211 participants received convalescent plasma. We found one randomised controlled trial ((RCT) 103 participants; 52 participants received convalescent plasma). RCTs are clinical studies where people are randomly allocated to receive the treatment (intervention group) or to receive a different treatment or no treatment (control group). RCTs produce the best evidence. We found three controlled non-randomised studies of interventions ((controlled NRSIs) 236 participants; 55 participants received convalescent plasma). These controlled NRSIs did not randomly allocate participants but did include a control group of participants who did not receive convalescent plasma. The remaining 16 studies (5201 participants) were not randomised and did not include a control group (non-controlled NRSIs) but provided information about unwanted effects of convalescent plasma.

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To assess whether convalescent plasma is an effective treatment for COVID-19, we evaluated results from the RCT and three controlled NRSIs. The control groups received standard care at the time of treatment without convalescent plasma. There was not enough evidence to determine whether or not convalescent plasma affected the risk of death due to any cause at hospital discharge, time to death, or need for breathing support. To assess whether convalescent plasma causes unwanted effects, we also evaluated the 16 non-controlled NRSIs (5201 participants). We identified some serious unwanted effects, which could be related to convalescent plasma, including death, allergic reactions or respiratory complications. We are very uncertain whether or not convalescent plasma affects the number of serious unwanted events.
None of the included studies reported effects on quality of life.

Certainty of the evidence

Our certainty (confidence) in the evidence was very limited because there was only one randomised study and most studies did not use reliable methods to measure their results. Furthermore, participants received various treatments alongside convalescent plasma, and some had underlying health problems.

Conclusion

We are very uncertain whether plasma from people who have recovered from COVID-19 is an effective treatment for people hospitalised with COVID-19. We are very uncertain whether or not convalescent plasma affects the number of serious harms. These findings could be related to the natural progression of the disease, other treatments that the participants received, or to convalescent plasma. Our searches found 98 ongoing studies evaluating convalescent plasma and hyperimmune immunoglobulin, of which 50 are randomised. This is the first living update of our review, and we will continue to update this review with results from completed studies.

How accurate are rapid tests, performed during a health-care visit (point-of-care), for diagnosing COVID-19?

Authors: Dinnes J, Deeks JJ, Adriano A, Berhane S, Davenport C, Dittrich S, Emperador D, Takwoingi Y, Cunningham J, Beese S, Dretzke J, Ferrante di Ruffano L, Harris IM, Price MJ, Taylor-Phillips S, Hooft L, Leeflang MMG, Spijker R, Van den Bruel A

Why is this question important?

People with suspected COVID-19 need to know quickly whether they are infected, so that they can self-isolate, receive treatment, and inform close contacts. Currently, COVID-19 infection is confirmed by sending away samples, taken from the nose and throat, for laboratory testing. The laboratory test, called RT-PCR, requires specialist equipment, may require repeat healthcare visits, and typically takes at least 24 hours to produce a result.
Rapid point-of-care tests can provide a result 'while you wait', ideally within two hours of providing a sample. This could help people isolate early and reduce the spread of infection.

What did we want to find out?

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We were interested in two types of rapid point-of-care tests, antigen and molecular tests. Antigen tests identify proteins on the virus, often using disposable devices. Molecular tests detect the virus's genetic material, using small portable or table-top devices. Both test the same nose or throat samples as RT-PCR tests.
We wanted to know whether rapid point-of-care antigen and molecular tests are accurate enough to replace RT-PCR for diagnosing infection, or to select people for further testing if they have a negative result.

What did we do?

We looked for studies that measured the accuracy of rapid point-of-care tests compared with RT-PCR tests to detect current COVID-19 infection. Studies could assess any rapid antigen or molecular point-of-care test, compared with a reference standard test. The reference standard is the best available method for diagnosing the infection; we considered RT-PCR test results and clinically defined COVID-19 as reference tests. People could be tested in hospital or the community. Studies could test people with or without symptoms.
Tests had to use minimal equipment, be performed safely without risking infection from the sample, and have results available within two hours of the sample being collected. Tests could be used in small laboratories or wherever the patient is (in primary care, urgent care facilities, or in hospital).

How did studies assess diagnostic test accuracy?

Studies tested participants with the rapid point-of-care tests. Participants were classified as known to have – and not to have - COVID-19, by RT-PCR in all studies. Studies then identified false positive and false negative errors in the point-of-care test results, compared to RT-PCR. False positive tests incorrectly identified COVID-19 when it was not present, potentially leading to unnecessary self-isolation and further testing. False negatives missed COVID-19 when it was present, risking delayed self-isolation and treatment, and spread of infection.

What we found

We found 18 relevant studies. Ten studies took place in North America, four in Europe, two in South America, one in China and one in multiple countries.
Nine studies deliberately included a high percentage of people with confirmed COVID-19 or included only people with COVID-19. Fourteen studies did not provide any information about the people providing the samples for testing and 12 did not provide any information about where people were tested.
None of the studies reported includedsamples from people without symptoms.

Main results

Five studies reported eight evaluations of five different antigen tests. Overall, there was considerable variation between the results of the antigen tests in how well they detected COVID-19 infection. Tests gave false positive results in less than 1% of samples.
Thirteen evaluations of four different molecular tests correctly detected an average of 95% of samples with COVID-19 infection. Around 1% of samples gave false positive results.
If 1000 people had molecular tests, and 100 (10%) of them really had COVID-19:
- 105 people would test positive for COVID-19. Of these, 10 people (10%) would not have COVID-19 (false positive result).
- 895 people would test negative for COVID-19. Of these, 5 people (1%) would actually have COVID-19 (false negative result).

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We noted a large difference in COVID-19 detection between the two most commonly evaluated molecular tests.

How reliable were the results of the studies?

Our confidence in the evidence is limited.

- Three-quarters of studies did not follow the test manufacturers' instructions, so may have found different results if they had.
- Often, studies did not use the most reliable methods or did not report enough information for us to judge their methods. This may have affected estimates of test accuracy, but it is impossible to identify by how much.
- A quarter of studies were published early online as 'preprints' and are included in the review. Preprints do not undergo the normal rigorous checks of published studies, so we are uncertain how reliable they are.

What are the implications of this review?

Studies provided little information about their participants, so it is not possible to tell if the results can be applied to people with no symptoms, mild symptoms, or who were hospitalised with COVID-19. Accurate rapid tests would have the potential to select people for RT-PCR testing or to be used where RT-PCR is not available. However, the evidence currently is not strong enough and more studies are urgently needed to be able to say if these tests are good enough to be used in practice.

How up-to-date is this review?

This review includes evidence published up to 25 May 2020. Because new research is being published in this field, we will update this review soon.

If you have any questions or comments with regard to the above document please feel free to contact me.

Kind regards

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