EUROPEAN REVIEW
COVID-19 VOLUME 2 TREATMENT

KORIAN FOUNDATION FOR AGEING WELL

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COVID-19 VOLUME 3
IMMUNITY AND TESTING

For this 3rd COVID Review, the Korian Foundation team and the Korian France Medical Department have once again mobilised to carry out a quality scientific watch to help professionals better understand this virus.

After a Volume 1 dedicated to symptomatology, and a Volume 2 dedicated to clinical trials carried out on the different treatment options, we have focused our Review on the state of scientific knowledge on immunity and testing. In fact, pending a large vaccination coverage, only tests are today effective in detecting and isolating early positive individuals, in order to break the chain of transmission and reduce the spread of the virus.

The next volume of our COVID Review will be devoted to vaccines and will be published in March. We wish you a good read!

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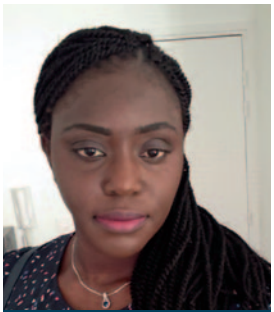

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SUMMARY IMMUNITY AND TESTING

DIAGNOSTIC TESTS: WHICH METHOD, WHICH PRECISION, WHICH STRATEGY?

IMMUNE MEMORY AFTER SARS-COV-2 INFECTION

MARCH 2021
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DIAGNOSTIC TESTS: WHICH METHOD, WHICH PRECISION, WHICH STRATEGY?

Antibody tests for identification of current and past infection with Sars-Cov-2 (Review)

Jonathan J Deeks & al.

Cochrane Library - June, 25th 2020

ABSTRACT

Background

In SARS-CoV-2 infections, serological tests for the presence of anti-SRAS-CoV-2 antibodies are intended to identify a previous SARS-CoV-2 infection and can help confirm the presence of a current infection.

Objective

The aim of this Cochrane review is to evaluate the accuracy of serological tests in the diagnosis of COVID-19 (recent or past Sars COV-2 infection) and in seroprevalence surveys.

Conclusions

- The sensitivity of serologies is too low during the first week after the beginning of symptoms to have a major role in the diagnosis of COVID-19,
- These tests have diagnostic value in the case of a negative rt-PCR if used from the 15th day of the beginning of symptoms.
- However, the duration of the antibody increase is currently unknown. The authors found very little data beyond 35 days after the beginning of symptoms. Therefore, the usefulness of these tests for seroprevalence surveys for public health management purposes is not known.
- Among the biases identified, the evaluation of sensitivity, mainly in hospital environments, does not indicate whether the tests are capable of detecting lower antibody levels that might be observed with a milder or even asymptomatic COVID-19 disease.
- In addition, there is a need to improve the quality of reporting of these tests in order to provide more data on the length of time the infection has been present.

KEY WORDS serological tests sensitivity recent or old COVID infection age of infection

https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013652/full

DIAGNOSTIC TESTS: WHICH METHOD, WHICH PRECISION, WHICH STRATEGY?

Accuracy of UK Rapid Test Consortium (UK-RTC) "AbC-19 Rapid Test" for detection of previous SARS-CoV-2 infection in key workers: test accuracy study

R. Mulchandani, H.E Jones, S. Taylor-Phillips, J. Shute, K. Perry, S. Jamarani, T. Brooks, A. Charlett, M. Hickman, I. Oliver, S. Kaptoge, J. Danesh, E. Di Angelantonio, A.E. Ades, D.H. Wyllie on behalf of the EDSAB-HOME and COMPARE Investigators

The BMJ - November, 11th 2020

ABSTRACT

After infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), most, but not all, infected people generate antibodies. Several pregnancy test format devices that can deliver testing rapidly and at scale– have recently become available that detect antibodies against SARS-CoV-2 proteins. These devices have two potential main uses: population serosurveillance and assessment of individual risk of developing immunity to coronavirus disease 2019 (covid-19). However, the use and utility of those test is limited by their efficiency and accuracy. Most studies evaluating accuracy of SARS-CoV-2 antibody tests have used a "two gate" or "diagnostic case-control" design, but this study design has been associated with overestimation of test accuracy. The authors assess the accuracy of the AbC-19 Rapid Test through a new design.

The authors collected 2847 blood samples in England in June 2020 (268 with a previous polymerase chain reaction (PCR) positive result and 2579 with unknown previous infection status); and 1995 prepandemic blood donors. AbC-19 and the Roche Elecsys antinucleoprotein assay, a highly sensitive laboratory immunoassay, where used ont hose samples. In this design the authors were able to proceed a "diagnostic case-control" study on the PCR + sample compared to the pre-pandemic samples. But they also conduct a "cohort" study on all the 2020 samples using the Roche test as a control. This design allows the assement of false-positiv.

Using an immunoassay reference standard, sensitivity was 94.2% (90.7% to 96.5%) among PCR confirmed cases but 84.7% (80.6% to 88.1%) among other people with antibodies. This is consistent with AbC-19 being more sensitive when antibody concentrations are higher, as people with PCR confirmation tended to have more severe disease. The probability that a positive result was correct would be 81.7% (76.8% to 85.8%).

TO REMEMBER

AbC-19 sensitivity was lower among unselected populations than among PCR confirmed cases of SARS-CoV-2, highlighting the scope for overestimation of assay performance in studies involving only PCR confirmed cases, owing to "spectrum bias." Assuming that 10% of the tested population have had SARSCoV-2 infection, around one in five key workers testing positive with AbC-19 would be false positives.

KEY WORDS antigenic test | Approach two gate/case-control design

https://www.bmj.com/content/371/bmj.m4262

DIAGNOSTIC TESTS: WHICH METHOD, WHICH PRECISION, WHICH STRATEGY?

SARS-CoV-2 detection with the SHERLOCK One-Pot rapid test (based on CRISPR)

Julia Joung, Alim Ladha, Makoto Saito, Nam-Gyun Kim, Ann E. Woolley, Michael Segel, Robert P.J. Barretto, Amardeep Ranu, Rhiannon K. Macrae, Guilhem Faure, Eleonora I. Ioannidi, Rohan N. Krajeski, Robert Bruneau, Meei-Li W. Huang, Xu G. Yu, Jonathan Z. Li, Bruce D. Walker, Deborah T. Hung, Alexander L. Greninger, Keith R. Jerome, Jonathan S. Gootenberg, Omar O. Abudayyeh, Feng Zhang

The New England journal of medicine - October, 8th 2020

ABSTRACT

CRISPR (clustered regularly interspaced short palindromic repeats)–based diagnostic tests collectively provide a nascent platform for the detection of viral and bacterial pathogens. Methods such as SHERLOCK (specific high-sensitivity enzymatic reporter unlocking), which typically use a two-step process (target amplification followed by CRISPR-mediated nucleic acid detection), have been used to detect SARS-CoV-2.

In this article, authors describe a simple test for detection of SARS-CoV-2. The sensitivity of this test is similar to that of reverse-transcription–quantitative polymerase-chain-reaction (RT-qPCR) assays. STOP (SHERLOCK testing in one pot) is a streamlined assay that combines simplified extraction of viral RNA with isothermal amplification and CRISPR-mediated detection. This test can be performed at a single temperature in less than an hour and with minimal equipment. The integration of isothermal amplification with CRISPR-mediated detection required the development of a common reaction buffer that could accommodate both steps. To amplify viral RNA, authors chose reverse transcription followed by loop-mediated isothermal amplification (LAMP) because LAMP reagents are widely available and use defined buffers that are amenable to Cas enzymes.

In blinded testing at an external laboratory at the University of Washington, they tested 202 SARS-CoV-2–positive and 200 SARS-CoV-2–negative nasopharyngeal swab samples obtained from patients. These samples were prepared by adding 50 µl of swab specimens obtained from patients with Covid-19 to a clean swab, in accordance with the recommendation of the Food and Drug Administration for simulating whole swabs for regulatory applications.

This testing showed that STOPCovid.v2 had a sensitivity of 93.1% and a specificity of 98.5%. STOPCovid.v2 false negative samples had RT-qPCR Ct values greater than 37. Positive samples were detected in 15 to 45 minutes.

TO REMEMBER

In this article, the authors demonstrated a method for detecting the SARS-Cov 2 virus in biological samples other than RT-PCR. This so-called STOP test (SHERLOCK in a jar test) which combines the simplified extraction of viral RNA with isothermal amplification and detection mediated by CRISPR has a sensitivity of 93.1% and a specificity of 98.5%. In addition, results can be obtained in 15-45 minutes.

KEY WORDS SARS –Cov 2 test STOP (SHERLOCK testing in one pot) loop-mediated isothermal amplification (LAMP)

https://www.nejm.org/doi/full/10.1056/NEJMc2026172

DIAGNOSTIC TESTS: WHICH METHOD, WHICH PRECISION, WHICH STRATEGY?

Use of exhaled breath condensate (EBC) in the diagnosis of SARS-COV-2 (COVID-19)

Ryan DJ, Toomey S, Madden SF, et al.

BMJ Thorax 2020 - November 2020

ABSTRACT

The diagnosis of COVID-19 is based on the detection of SARS-CoV-2 viral RNA by reverse transcription PCR (RT-PCR) from nasopharyngeal swabs.
If there is a strong suspicion of COVID-19 in a patient with a negative nasopharyngeal swab, lower airway sampling is recommended. The use of the exhaled breath technique can be an alternative to bronchoalveolar lavage and tracheal aspirations, which are invasive techniques.
The study described in the article is a prospective observational and effectiveness evaluation study.
Of the 40 patients recruited, 31 had a diagnosis of COVID-19, 16 of them (40%) had a positive nasopharyngeal swab and 15 (37.5%) a negative swab.
In the 15 COVID-19 patients with a negative nasopharyngeal swab, rt-PCR on exhaled breath was positive in 10 (66.6%) to 14 (93.3%) patients depending on the type of test (number of genes) used.

TO REMEMBER

This study provides promising results on the realisation of rt-PCR on exhaled breath. It is an effective and non-invasive method for identifying SARS-CoV-2 from samples of the lower respiratory tract. It should be considered as a complementary investigation facilitating the diagnosis of COVID-19 in patients with suspected infection and negative nasopharyngeal swabs.

KEY WORDS RT-PCR exhaled breath nasopharyngeal swabs

https://thorax.bmj.com/content/76/1/86.long

DIAGNOSTIC TESTS: WHICH METHOD, WHICH PRECISION, WHICH STRATEGY?

Thoracic imaging tests for the diagnosis of COVID-19 (Review)

Islam N, Salameh JP, Leeflang MMG, Hoo! L, McGrath TA, van der Pol CB, Frank RA, Kazi S, Prager R, Hare SS, Dennie C, Spijker R, Deeks JJ, Dinnes J, Jenniskens K, Korevaar DA, Cohen JF, Van den Bruel A, Takwoingi Y, van de Wijgert J, Wang J, McInnes MDF, Cochrane COVID-19 Diagnostic Test Accuracy Group

Cochrane library - November, 26th 2020

ABSTRACT

The respiratory illness caused by SARS-CoV-2 infection continues to present diagnostic challenges. Early research showed thoracic (chest) imaging to be sensitive but not specific in the diagnosis of coronavirus disease 2019 (COVID-19). However, this is a rapidly developing field and these findings need to be re-evaluated in the light of new research.This update focuses on people suspected of having COVID-19 and excludes studies with only confirmed COVID-19 participants. Main objective was to evaluate the diagnostic accuracy of thoracic imaging (computed tomography (CT), X-ray and ultrasound) in people with suspected COVID-19. The authors searched the COVID-19 Living Evidence Database from the University of Bern, the Cochrane COVID-19 Study Register, The Stephen B. Thacker CDC Library, and repositories of COVID-19 publications through to 22 June 2020. They did not apply any language restrictions. The authors screened studies, extracted data, and assessed the risk of bias and applicability concerns using the QUADAS-2 domain-list independently, in duplicate. They categorized included studies into three groups based on classification of index test results: studies that reported specific criteria for index test positivity (group 1); studies that did not report specific criteria, but had the test reader(s) explicitly classify the imaging test result as either COVID-19 positive or negative (group 2); and studies that reported an overview of index test findings, without explicitly classifying the imaging test as either COVID-19 positive or negative (group 3).

They included 34 studies: 30 were cross-sectional studies with 8491 participants suspected of COVID-19, of which 4575 (54%) had a final diagnosis of COVID-19; four were case-control studies with 848 cases and controls in total, of which 464 (55%) had a final diagnosis of COVID-19. Chest CT was evaluated in 31 studies (8014 participants, 4224 (53%) cases), chest X-ray in three studies (1243 participants, 784 (63%) cases), and ultrasound of the lungs in one study (100 participants, 31 (31%) cases). Twenty-six percent (9/34) of all studies were available only as preprints. Nineteen studies were conducted in Asia, 10 in Europe, four in North America and one in Australia. Sixteen studies included only adults, 15 studies included both adults and children and one included only children. Two studies did not report the ages of participants. Twenty-four studies included inpatients; four studies included outpatients, while the remaining six studies were conducted in unclear settings. The majority of included studies had a high or unclear risk of bias with respect to participant selection, index test, reference standard, and participant flow. For chest CT in suspected COVID-19 participants (31 studies, 8014 participants, 4224 (53%) cases) the sensitivity ranged from 57.4% to 100%, and specificity ranged from 0% to 96.0%. The pooled sensitivity of chest CT in suspected COVID-19 participants was 89.9% (95% CI 85.7 to 92.9) and the pooled specificity was 61.1% (95% CI 42.3 to 77.1).

Sensitivity analyses showed that when the studies from China were excluded, the studies from other countries demonstrated higher specificity compared to the overall included studies. When studies that did not classify index tests as positive or negative for COVID-19 (group 3) were excluded, the remaining studies (groups 1 and 2) demonstrated higher specificity compared to the overall included studies. Sensitivity analyses limited to cross-sectional studies, or studies where at least two RT-PCR tests were conducted if the first was negative, did not substantively alter the accuracy estimates. We did not identify publication status as a source of heterogeneity. For chest X-ray in suspected COVID-19 participants (3 studies, 1243 participants, 784 (63%) cases) the sensitivity ranged from 56.9% to 89.0% and specificity from 11.1% to 88.9%. The sensitivity and specificity of ultrasound of the lungs in suspected COVID-19 participants (1 study, 100 participants, 31 (31%) cases) were 96.8% and 62.3%, respectively. We could not perform a meta-analysis for chest X-ray or ultrasound due to the limited number of included studies.

TSVP →

TO REMEMBER

These findings indicate that chest CT is sensitive and moderately specific for the diagnosis of COVID-19 in suspected patients, meaning that CT may have limited capability in differentiating SARS-CoV-2 infection from other causes of respiratory illness. However, authors are limited in their confidence in these results due to the poor study quality and the heterogeneity of included studies. Because of limited data, accuracy estimates of chest X-ray and ultrasound of the lungs for the diagnosis of suspected COVID-19 cases should be carefully interpreted. Future diagnostic accuracy studies should pre-define positive imaging findings, include direct comparisons of the various modalities of interest on the same participant population, and implement improved reporting practices. Planned updates of this review will aim to: increase precision around the accuracy estimates for chest CT (ideally with low risk of bias studies); obtain further data to inform accuracy of chest X-rays and ultrasound; and obtain data to further fulfil secondary objectives (e.g. 'threshold' effects, comparing accuracy estimates across different imaging modalities) to inform the utility of imaging along different diagnostic pathways.

KEY WORDS SARS-CoV-2 test, X-RAY thoracic imaging

https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013639.pub3/full

DIAGNOSTIC TESTS: WHICH METHOD, WHICH PRECISION, WHICH STRATEGY?

Routine laboratory testing to determine if a patient has COVID-19

Inge Stegeman, Eleanor A Ochodo, Fatuma Guleid, Gea A. Holtman, Bada Yang, Clare Davenport, Jonathan J Deeks, Jacqueline Dinnes, Sabine Dittrich, Devy Emperador, Lotty Hoo, René Spijker, Yemisi Takwoingi, Ann Van den Brue, Junfeng Wang, Miranda Langendam, Jan Y Verbakel, Mariska MG Leeflang, Cochrane COVID-19 Diagnostic Test Accuracy Group

Cochrane library - November, 19th 2020

ABSTRACT

Specific diagnostic tests to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and resulting COVID-19 disease are not always available and take time to obtain results. Routine laboratory markers such as white blood cell count, measures of anticoagulation, C-reactive protein (CRP) and procalcitonin, are used to assess the clinical status of a patient. These laboratory tests may be useful for the triage of people with potential COVID-19 to prioritize them for different levels of treatment, especially in situations where time and resources are limited. The main objective was to assess the diagnostic accuracy of routine laboratory testing as a triage test to determine if a person has COVID-19.

On 4 May 2020, the teams undertook electronic searches in the Cochrane COVID-19 Study Register and the COVID-19 Living Evidence Database from the University of Bern, which is updated daily with published articles from PubMed and Embase and with preprints from medRxiv and bioRxiv. Authors did not apply any language restrictions. They included both case-control designs and consecutive series of patients that assessed the diagnostic accuracy of routine laboratory testing as a triage test to determine if a person has COVID-19. The reference standard could be RT-PCR alone; RT-PCR plus clinical expertise or and imaging; repeated RT-PCR several days apart or from different samples; WHO and other case definitions; and any other reference standard used by the study authors. Two review authors independently extracted data from each included study. They also assessed the methodological quality of the studies, using QUADAS-2. J

21 studies were included in this review: 14126 COVID-19 patients and 56585 non-COVID-19 patients in total. Studies evaluated a total of 67 different laboratory tests. Although, authors were interested in the diagnostic accuracy of routine tests for COVID-19, the included studies used detection of SARS-CoV-2 infection through RT-PCR as reference standard. There was considerable heterogeneity between tests, threshold values and the settings in which they were applied. For some tests, a positive result was defined as a decrease compared to normal values, for other tests a positive result was defined as an increase, and for some tests both increase and decrease may have indicated test positivity. None of the studies had either low risk of bias on all domains or low concerns for applicability for all domains. Only three of the tests evaluated had a summary sensitivity and specificity over 50%. These were: increase in interleukin-6, increase in C-reactive protein and lymphocyte count decreas.

TO REMEMBER

Although these tests give an indication about the general health status of patients and some tests may be specific indicators for inflammatory processes, none of the tests investigated are useful for accurately ruling in or ruling out COVID-19 on their own. Studies were done in specific hospitalized populations, and future studies should consider non-hospital settings to evaluate how these tests would perform in people with milder symptoms.

KEY WORDS SARS-COV 2 tests, RT-PCR screening

https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013787/full

DIAGNOSTIC TESTS: WHICH METHOD, WHICH PRECISION, WHICH STRATEGY?

Rethinking the sensitivity of the Covid-19 test

Michael J. Mina, M.D., Ph.D., Roy Parker, Ph.D., and Daniel B. Larremore, Ph.D

The NEW ENGLAND JOURNAL of MEDICINE - November 26th 2020

ABSTRACT

The authors promote a change of perception regarding the sensitivity of Sars-Cov-2 detection tests. The tests currently validated and considered as the reference tests are designed to detect viral proteins or RNA molecules with the highest sensitivity without taking into account the context. The key question is not how well molecules can be detected in a single sample but how effectively infections can be detected in a population by the repeated use of a given test as part of an overall testing strategy, to break the chain of transmission and reduce the spread of the virus.

These tests should be designed for frequent use to identify infected and therefore contagious people at an early stage, especially in people with asymptomatic forms where rt-PCR positivity often occurs after the period of contagiousness, as evidenced by the low viral load. These tests, some of which are currently being tested, should complement, not replace, current clinical diagnostic tests. The optimal strategy would be to combine both types: frequent, inexpensive and rapid tests combined with standard tests to confirm the diagnosis.

Public awareness campaigns should also continue to inform the public that a negative test does not necessarily mean the absence of infection to encourage continued use of masks and respect for physical distancing.

TO REMEMBER

In order to defeat Covid-19, scientific bodies must encourage the evaluation of tests allowing rapid mass screening of Sars-Cov-2 at an early stage and thus limit its spread. To achieve this objective, these "rapid" tests must be cheap, easy to use and frequently used, even if their sensitivity is lower than the Gold Standard.

KEY WORDS Rapid tests sensitivity COVID-19 mass screening

https://www.nejm.org/doi/full/10.1056/NEJMp2025631

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IMMUNE MEMORY AFTER SARS-COV-2 INFECTION

Detection of SARS-CoV-2-Specific Humoral and Cellular Immunity in COVID-19 Convalescent Individuals

Ling Ni, Fang Ye, Meng-Li Cheng, Yu Feng, Yong-Qiang Deng, Hui Zhao, Peng Wei, Jiwan Ge, Mengting Gou, Xiaoli Li, Lin Sun, Tianshu Cao, Pengzhi Wang, Chao Zhou, Rongrong Zhang, Peng Liang, Han Guo, Xinquan Wang, Cheng-Feng Qin, Fang Chen, Chen Dong

Immunity 52, 971–977 - June 16th 2020

ABSTRACT

This study was carried out in order to better assess the immune responses, especially adaptive immune responses to SARS-CoV-2 infection.
Blood samples were collected from patients who had recovered from the SARS-CoV-2 infection.
These samples were used to analyse their SARS-CoV-2 specific antibody responses as well as their T lymphocyte responses.
These findings suggest both B and T cells participate in immune-mediated protection to viral infection. In addition, the neutralizing antibody titers significantly correlated with the numbers of NP-specific T cells (the nucleocapsid protein, most abundant protein in coronaviruses).
This work has thus provided a basis for further analysis of protective immunity to SARS-CoV-2 and understanding the pathogenesis of COVID-19.

TO REMEMBER

- SARS-CoV-2-specific antibodies are detected in COVID-19 convalescent subjects
- Most COVID-19 convalescent individuals have detectable neutralizing antibodies
- Cellular immune responses to SARS-CoV-2 are found in COVID-19 convalescent subjects
- Neutralization antibody titers correlate with the numbers of virus-specific T cells

KEY WORDS SARS-CoV2 COVID-19 patients adaptive immunity SARS-CoV-2-specific antibody SARS-CoV-2-specific T cells

https://doi.org/10.1016/j.immuni.2020.04.023

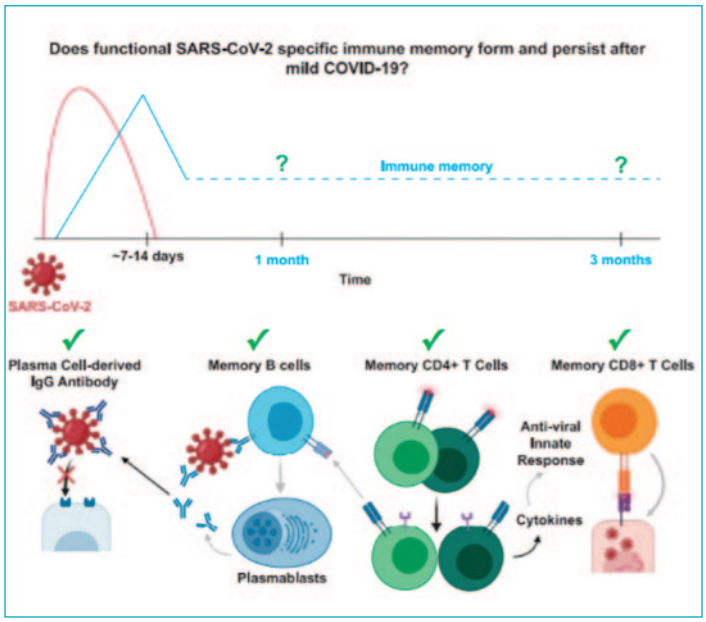
IMMUNE MEMORY AFTER SARS-COV-2 INFECTION

Functional SARS-CoV-2-Specific Immune Memory Persists after Mild COVID-19

Lauren B. Rodda, Jason Netland, Laila Shehata, Kurt B. Pruner, Peter A. Morawski, Christopher D. Thouvenel, Kennidy K. Takehara, Julie Eggenberger, Emily A. Hemann, Hayley R. Waterman, Mitchell L. Fahning, Yu Chen, Malika Hale, Jennifer Rathe, Caleb Stokes, Samuel Wrenn, Brooke Fiala, Lauren Carter, Jessica A. Hamerman, Neil P. King, Michael Gale, Jr., Daniel J. Campbell, David J. Rawlings, and Marion Pepper

Cell - November 23th 2020

ABSTRACT



In the majority of infection cases with the SARS-CoV-2 virus, infected individuals experience mildly symptomatic coronavirus disease. This raises the following question: does this form of infection induce a persistent immune memory that could contribute to immunity ?
This article describes a longitudinal assessment of individuals recovered from mild COVID-19 to determine whether they develop and sustain multifaceted SARS-CoV-2-specific immunological memory. Recovered individuals developed SARS-CoV-2-specific immunoglobulin (IgG) antibodies, neutralizing plasma, and memory B and memory T cells that persisted for at least 3 months. The data show that the number of SARS-CoV-2 specific IgG memory B cells has increased over time. Additionally, SARS-CoV-2-specific memory lymphocytes exhibited characteristics associated with potent antiviral function: memory T cells secreted cytokines and expanded upon antigen re-encounter, whereas memory B cells expressed receptors capable of neutralizing virus when expressed as monoclonal antibodies.
Therefore, mild COVID-19 elicits memory lymphocytes that persist and display functional hallmarks of antiviral immunity.

TO REMEMBER

- Longitudinal analysis of multifaceted immune memory following mild COVID-19
- Antibodies capable of neutralizing virus persist for at least 3 months in most subjects
- Virus-specific memory B and T cells display hallmarks of anti-viral immunity
- Memory B cells (MBCs) increase in number and express antibodies capable of neutralizing SARS-CoV-2

KEY WORDS SARS-CoV2 COVID-19 memory B cell memory T cell monoclonal antibody Human vaccine adaptive immune response

https://doi.org/10.1016/j.cell.2020.11.029

IMMUNE MEMORY AFTER SARS-COV-2 INFECTION

The dynamics of humoral immune responses following SARS-CoV-2 infection and the potential for reinfection

Paul Kellam, Wendy Barclay.

Journal of General Virology - August 2020

ABSTRACT

SARS-CoV-2 is a novel coronavirus that is the causative agent of coronavirus infectious disease 2019 (COVID-19). The timing, magnitude and longevity of humoral immunity is not yet understood for SARS-CoV-2. Nevertheless, understanding this is urgently required to inform the likely future dynamics of the pandemic, to guide strategies to allow relaxation of social distancing measures and to understand how to deploy limiting vaccine doses when they become available to achieve maximum impact. SARS-CoV-2 is the seventh human coronavirus to be described. Four human coronaviruses circulate seasonally and cause common colds. Two other coronaviruses, SARS and MERS, have crossed from animal sources into humans but have not become endemic. Here we review what is known about the human humoral immune response to epidemic SARS CoV and MERS CoV and to the seasonal, endemic coronaviruses. Then we summarize recent, mostly non-peer reviewed, studies into SARS-CoV-2 serology and reinfection in humans and non-human primates.

TO REMEMBER

Most people infected with SARS-CoV-2 show antibodies 10-14 days after infection. There is little information on the antibody response longevity to SARS-CoV-2, but antibodies to other human coronaviruses are known to decrease over time, and there are reports of reinfection with homologous coronaviruses after about 80 days.
Thus, re-infection of previously benign SARS-CoV-2 cases is a realistic possibility that should be considered in second-wave and post-pandemic models. People with low antibody titers after benign disease should be monitored for signs of re-infection and disease recurrence through regular clinical surveillance and diagnostic virus detection by RT-PCR.
It is likely that protective mechanisms through other arms of the immune response (memory and cytotoxic T cells) modify COVID-19 disease development upon re-infection by decreasing symptoms in the absence of protective antibodies or by increasing the nadir infection of the humoral immune response by under-neutralizing antibody titers.
It is also not known whether reinfections will lead to further transmission, but this cannot be ruled out. Assuming decreasing immunity, the models show that if immunity is not permanent, many epidemiological scenarios lead SARS-CoV-2 to become a seasonal, annual, biennial or sporadic human coronavirus with epidemic trends over the next 5 years.
While immunity to SARS-CoV-2 can be designed to be permanent through regular vaccination, models suggest that SARS-CoV-2 infection can be significantly reduced or eventually eliminated.

KEY WORDS SARS-CoV-2 COVID-19 serology reinfection antibodies

https://www.microbiologyresearch.org/content/journal/jgv/10.1099/jgv.0.001439

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IMMUNE MEMORY AFTER SARS-COV-2 INFECTION

Sex differences in the decline of neutralizing antibodies to SARS-CoV-2

Ludivine Grzelak, Aurélie Velay, Yoann Madec, Floriane Gallais, Isabelle Staropoli, Catherine Schmidt-Mutter, Marie-Josée Wendling, Nicolas Meyer, Cyril Planchais, David Rey, Hugo Mouquet, Ludovic Glady, Yves Hansmann, Timothée Bruel, Jérome De Sèze, Arnaud Fontanet, Maria Gonzalez, Olivier Schwartz, Samira Fafi-Kremer

MedRxiv preprint - November 15th 2020

ABSTRACT

The aim of the study carried out and presented in this article is to better characterise the humoral response evolution of SARS-CoV-2 in infected populations.

This article describes a longitudinal study of sera from 308 RT-qPCR+ individuals with the mild form of the disease, collected at two points in time, up to 6 months after the onset of symptoms.

In this study two serological tests were performed: an anti-S test (the Spike protein or S protein mediates receptor binding and membrane fusion) and an anti-N test (the nucleocapsid protein, N protein, is the most abundant protein in coronaviruses). In addition, neutralizing antibodies have been quantified.

At month 1 (M1), males, individuals > 50 years of age or with a body mass index (BMI) > 25 exhibited higher levels of antibodies. Then antibody levels decreased over time for all individuals. At M3-6, anti-S antibodies persisted in 99% of individuals while anti-N IgG were measurable in only 59% of individuals. The decline in anti-S and NAbs was faster in males than in females, independently of age and BMI.

This results show that some serology tests are less reliable overtime and suggest that the duration of protection after SARS-CoV-2 infection or vaccination will be different in women and men.

TO REMEMBER

- Antibody levels and neutralizing activity decrease in the weeks after infection
- Neutralizing antibody titers decreased at twice the rate of anti-S IgG
- There are gender differences in the longevity of the immune response, men showing higher levels of antibodies soon after infection, but a more pronounced decrease
- Women infected with SARS-CoV-2 have significantly more robust T-cell activation than men
- Some serological tests are less reliable over time and suggest that the duration of protection after an SARS-CoV-2 infection or vaccination will be different in women and men.

KEY WORDS SARS-CoV2 COVID-19 Neutralizing monoclonal antibodies Male adaptive immune response Female adaptive immune response

https://doi.org/10.1101/2020.11.12.20230466

IMMUNE MEMORY AFTER SARS-COV-2 INFECTION

Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity

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Cell - November 12th 2020

ABSTRACT

The adaptive immune system consists of three major lymphocyte types: B cells (antibody producing cells), CD4+ T cells (helper T cells), and CD8+ T cells (cytotoxic, or killer, T cells) (Murphy and Weaver, 2016). All three arms of adaptive immunity can be important in protection against viral infections. Most COVID-19 vaccine efforts focus on the elicitation of neutralizing antibodies, with additional interest in elicitation of CD4+ or CD8+ T cells. Almost all neutralizing antibody responses, durable antibody responses, and affinity-matured B cell memory depend on CD4+ T cell help.

Based on those conclusion and on some previons mouse-model study, the authors completed a combined examination of all three branches of adaptive immunity at the level of SARS-CoV-2-specific CD4+ and CD8+ T cell and neutralizing antibody responses in acute and convalescent subjects. SARS-CoV-2-specific CD4+ and CD8+ T cells were each associated with milder disease.

They investigated the immune responds in blood samples of 30 convalescent subject and 24 acute patients. The COVID-19 diseases severity were classed from mild to fatal. After a detailed analysis and descrition of each responses characteristics, the authors investigated the combinaison of all three.

Subject where categorized regarding the number of arms they had activated, and the authors underlines the following conclusions :

- SARS-CoV-2 antigenic specific adaptive immune respond limit COVID-19 disease severity
- Coordinated responses by all three branches of adaptive immunity were better than partial responses, with prominent roles for SARS-CoV-2-specific CD4+T cells associated with less COVID-19 disease severity
- CXCL10 may be a plasma marker in acute COVID-19 of impaired T cell responses.
- Aging and scarcity of naive T cells may be linked risk factors for failure to generate a coordinated response,resulting in increased susceptibility to severe COVID-19.

These findings have implications both for understanding COVID-19 immunity and pathology, as well as COVID-19 vaccine designs. Future studies will be required to test these relationships rigorously.

TO REMEMBER

Multiple coordinated arms of adaptive immunity control better than partial responses d CXCL10 may be a biomarker of impaired T cell responses in acute COVID-19

Aging and scarcity of naive T cells may be linked risk factors for severe COVID-19

KEY WORDS adaptive immune respond | lymphocyte T CD4+ | lymphocyte T CD8+ | neutrolizing antibodies

https://www.sciencedirect.com/science/article/pii/S0092867420312356

IMMUNE MEMORY AFTER SARS-COV-2 INFECTION

Immune Response and COVID-19: A mirror image of Sepsis

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ABSTRACT

The emergence of SARS-CoV-2 virus and its associated disease COVID-19 have triggered significant threats to public health, in addition to political and social changes. An important number of studies have reported the onset of symptoms compatible with pneumonia accompanied by coagulopathy and lymphocytopenia during COVID-19. Increased cytokine levels, the emergence of acute phase reactants, platelet activation and immune checkpoint expression are some of the biomarkers postulated in this context. As previously observed in prolonged sepsis, T-cell exhaustion due to SARS-CoV-2 and even their reduction in numbers due to apoptosis hinder the response to the infection. In this review, we synthesized the immune changes observed during COVID-19, the role of immune molecules as severity markers for patient stratification and their associated therapeutic options.

TO REMEMBER

The study of the immune system and the clotting cascade during a COVID-19 infection should be able to provide valuable information for the diagnosis and treatment of this disease. Many questions remain unanswered in COVID-19, such as "Can the evolution of COVID-19 patients be predicted by establishing their immune profiles on admission", "Could the expression of immune control points regulate the second phase of COVID-19? "and "Could immune control point inhibitors and their ligands be useful in the treatment of COVID-19 as they have been used in many types of cancer and as they have been hypothesised in septicaemia? The identification of these patients with poorer prognoses will therefore facilitate the development of targeted therapies.

KEY WORDS COVID-19 septicaemia immune response immune checkpoints T cell depletion

https://www.ijbs.com/v16p2479.htm

IMMUNE MEMORY AFTER SARS-COV-2 INFECTION

Covid-19: Perspectives on Innate Immune Evasion

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ABSTRACT

This article is a systematic review of SARS-CoV-2 actions against each immune response actors. The authors did a list works on of each immune mechanism implied the the response to coronavirus infections but also of escape process used by the virus against those mechanism. All studies and molecular process are described in order to target the best pathways for increase the patient's prognostic. Coronaviral infections are enabled by potent immunoevasory mechanisms that target multiple aspects of innate immunity, with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) able to induce a cytokine storm, impair interferon responses, and suppress antigen presentation on both MHC class I and class II. The COVID-19 is able to escape specific antibodies by hiding it interaction domain but also to create a inflammatory respond that affect it host cells. SARS-CoV-2's biology is it resulting immune responses, immunopathology, and immune evasion mechanisms. Authors underlines : - how SARS-CoV-2 modifies gene expression in innate immune cells - Addressing IFN evasion mechanisms and preventing viral immune evasion - While a major driver of the cytokine storm in COVID-19 patients, IL-6 has both pro- and anti-inflammatory properties, giving it a complex role in COVID-19 pathology. Understanding the immune responses to SARS-CoV-2 and its immunoevasion approaches will improve our understanding of pathogenesis, virus clearance, and contribute toward vaccine and immunotherepeutic design and evaluation.

TO REMEMBER

Currently, there are no approved drugs or vaccines to treat human CoVs, but recent advances in our understanding of the immune response and immune evasion mechanisms of CoV's
opens up many therapeutic avenues. These include mechanisms for limiting viral entry and replication, promoting viral clearance, and inducing productive anti-CoV immune responses. Investigating how SARS-CoV-2 modifies gene expression in innate immune cells will be crucial to identifying immune mechanisms that could be modulated to improve patient outcomes. Addressing IFN evasion mechanisms and preventing viral immune evasion may contribute to enhancing viral clearance and lessening immunopathology. Inhibition of IL-6 signaling and elucidation of the mechanism which elevates IL-6 in patients will help to find new potential strategies to reduce pathology during COVID-19 infection. Finally, newly available tools such as next generation sequencing will provide key information on the clinical features of the disease and potential targets for the development of drugs and vaccines. While an effective treatment for COVID-19 remains elusive, this large array of tools and knowledge should enable the rapid development of preventative and therapeutic treatments for this newly emerged disease.

KEY WORDS SARS-CoV-2 macrophahge innate immunity cytokine major histocompatibility complex

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