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Latest News on COVID-19

THE OBSTACLE COURSE OF SEROLOGICAL TESTS, VIRAL REINFECTION, AND REACTIVATION.

With more than 3,000,000 cases and 200,000 deaths, and after three months of worldwide outbreak, scientists keep on learning about COVID-19 every day.

How can people be positively diagnosed twice to COVID? Are serological diagnostic tests 100% reliable? Which part of the population is more likely to be infected?

Let's review the latest updates on what we know about this challenging virus, and the on-going assay developments.

1. The obstacle course of serological tests

The last few months have seen the fast emergence of rapid molecular tests to test presence of virus RNA in patients. Today, it's the turn of serological tests to take centre stage. With serological tests, the aim is now to measure host immunity to the virus. But the game isn't won yet, and many challenges stand in the way of success:

- **Specificity:** Many seasonal coronavirus (HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63) that cause colds circulate around the globe. They are not genetically identical to COVID-19, but sufficiently enough to give a false positive in case of low specificity tests.
- **Sensitivity:** A test with low sensitivity - despite a great specificity for the COVID-19 strain - could miss a weak immune response, and so provides a false negative result. A Chinese cohort of 175 patients demonstrated that immune response was highly variable and undetectable in 6% of the cases (*Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications - Fan Wu, Aojie Wang, Mei Liu, Qimin Wang, Jun Chen*).
- **Timing:** If people have been infected less than 12 days ago, the seroconversion mechanism hasn't occurred yet. You're just measuring no biological material at all during the incubation phase.
- **Individual targeted epitopes:** It's also possible that some individuals are developing antibodies against a different viral protein than the one of the test. Nevertheless, it has been reported that antibodies targets are mainly full-length S protein and its receptor-binding domain (*A serological assay to detect SARS-CoV-2 seroconversion in humans, Fatima Amanat, Daniel Stadlbauer, Shirin Strohmeier*).
- **And finally:** you need to show the relationship between seroconversion and seroneutralization. If patients are producing specific antibodies against COVID-19, in sufficient amounts, against the tested epitope, how can we be sure these antibodies are protective?

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2. All men are created equal. Are you sure?

- **Hypertension, cardiovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and chronic kidney disease are aggravating factors** of COVID-infected patients' conditions (*Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis. Arch Acad Emerg Med. 2020;8 (1):e35*).
- **Men are more sensitive than women** (*Based upon the data of the WHO website*), 63% of all deaths were men). **Oestrogen concentration? X chromosome?** For the moment, we don't have a clue about the root cause of such a difference, but this question should be addressed in the context of vaccine development.
- **Children seem to be less affected by COVID-19 than adults.** In a large report gathering 72 314 cases in China, only 2% were under 19 years old. Another report confirms that no ICU admissions or deaths were reported among persons aged ≤19 years in the USA (*Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020*). **How can we explain this fact?** One hypothesis is that children present less ACE-2 receptors and so less potential cell entries for the virus. We may also suggest that a young immune system doesn't present the same features as a mature one. The level of antibodies could be lower and the risk of cytokine storm syndrome decreased.

3. Positively diagnosed to COVID-19. Not once, but twice!

Recently, South Korea reported some cases of cured patients tested positive to Covid-19. The Korea Centers for Disease Control and Prevention explained that of 7,829 people who have recovered from coronavirus, 2.1% were positively retested (163 cases). **How is this possible?**

- One hypothesis is reactivation. The coronavirus could remain latent in the body and attack the respiratory organs again once it is reactivated. So far, this hypothesis has not been proven, and experts of HIV and HPV are not really in favour of such an option.

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- Another explanation lies in the accuracy of diagnostic kits:
  - Poor quality of the components of the test can be blamed. Nevertheless, regarding the offer on the market for such tests, and the level of expertise in South Korea in biotechnology field, we can be confident that the country has access to a large number of high-quality grade tests.
  - Mutation of the virus may be an option. In fact, it's unlikely that COVID-19 has already mutated in a drastic way. What's in it for COVID at the moment if it mutates? It is spreading so easily among the worldwide population, there's no necessity to change what already works pretty well.
- We might also suggest that fragments of the virus remain in the body. In fact, despite the seroconversion and the cured state of the patient, some residual virus RNA can persist in the bloodstream.
- Reinfection is another possibility. Some people with underlying weak immune system conditions, and presenting lower antibody levels, could face a second infection to the virus. Nevertheless, regarding the antibody immune response of patients, the probability of such event is estimated as being low.

It is clear that we are still in the early stages of our coronavirus discoveries. The obstacles of accuracy in serological tests are numerous, some subset populations present higher risks and the viral reactivation is not so clear for the moment.

However, we need to make decisions without full knowledge of the immunity of COVID-19. The stakes are too high to sit back and do nothing...

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