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Morning Brief : Scientific Review

(20 April 2020)

The purpose of the Morning Brief is to **summarise** and present key information, research articles and other relevant publications pertaining to critical care and COVID-19. We aim to prioritise information, articles and publications released in the preceding 24-48 hours

Stellenbosch University Research Response Team

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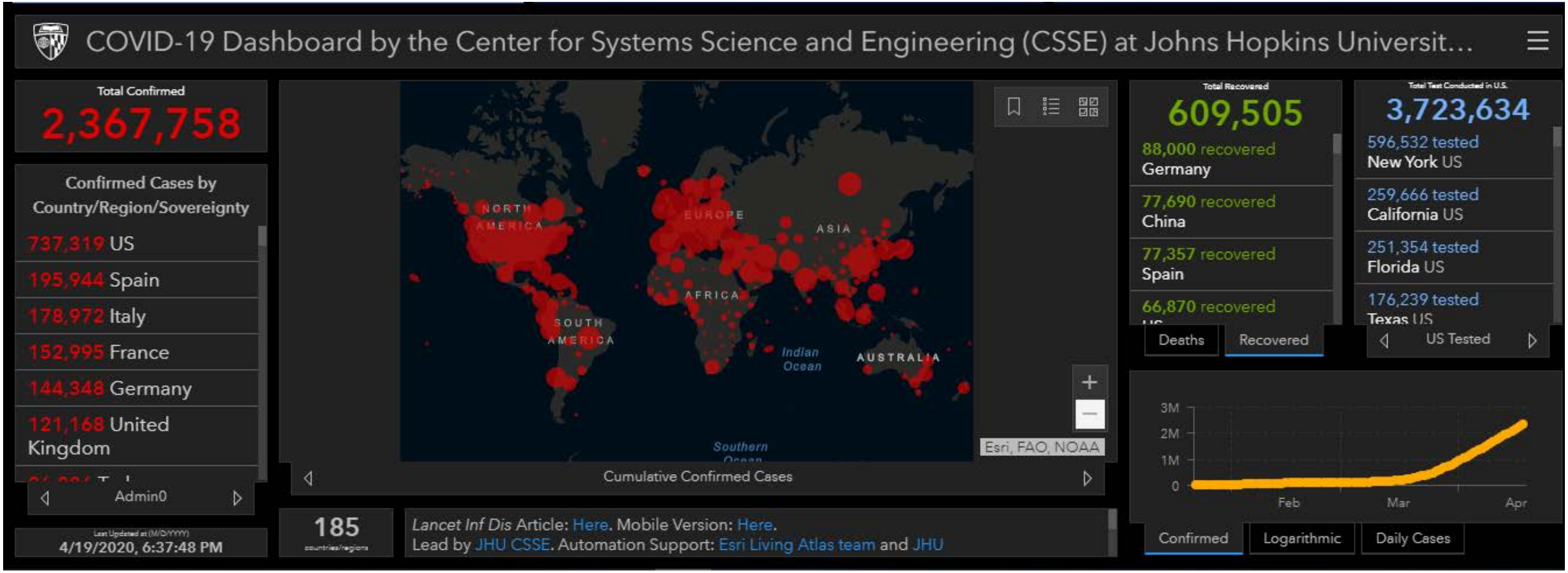
Content

- Daily Statistics (Global update)
- Daily Statistics (South African update)
- Articles of interest
- References

Global Update



Accessed at 19:19 on 19 April 2020
Source: https://coronavirus.jhu.edu/map.html

South African Update

Observations on deceased patients:
Majority of deceased patients have been elderly people and people with comorbidities – consistent with trends seen globally

Testing:
Daily testing has increased – South Africa is leading in terms of testing
(Reported testing excludes repeat testing done on one individual)

The provincial breakdown is as follows:

GAUTENG	1101
WESTERN CAPE	836
KWAZULU – NATAL	604
EASTERN CAPE	270
FREE STATE	100
LIMPOPO	26
NORTH WEST	24
MPUMALANGA	25
NORTHERN CAPE	16
UNALLOCATED	32

COVID-19 Statistics in South Africa

108021	3034	903	52
Tests Conducted	Positive Cases Identified	Recoveries	Deaths

Accessed at 19:27 on 19 April 2020
Source: https://sacoronavirus.co.za/2020/04/18/update-on-covid-19-18th-april-2020/

Articles of interest

Summary

- What do PCR and serology tests measure?
  - PCR detects viral nucleic acid (RNA), while serology tests measure antibodies produced in response to the infection
- Role of IgG, IgM or IgA?
  - Humoral response to the infection
  - Seroconversion rate: IgM & IgA (5 days (IQR, 3-6), IgG (14 days (IQR, 10-18)
  - Positive IgM could represent an early infection, while positive IgG could represent past infection or late stage of infection
  - Combination of IgG and IgM are recommended
- RNA test + Antibody tests yielded better sensitivity
- Why does seroconversion lag behind a positive PCR test?
  - Seroconversion lag: Might represent insufficient antibody to be detected in early infection, or failure of patients to generate antibody response
- How long do antibody tests remain positive?
  - How long the antibodies could last remains unknown
- What does positive serology, negative PCR mean?
  - Might suggest false negative by PCR due to sampling process
- Benefits of antibody tests
  - Faster turn-around time, high-throughput and less workload
  - Mass testing
- Limitations of antibody tests
  - Cross-reactivity (False-positive results)
  - False negative (In early infection or in those failing to generate antibody response)
- WHO on antibody tests: Scientific brief (8 April 2020)
  - Based on current data, the use of antibody diagnostic tests are not recommended by WHO for patient care, but continuation of work to establish their usefulness in disease surveillance and epidemiologic research is encouraged
  - Target product profiles for desired COVID-19 diagnostics are in development.
  - WHO will continue to work to develop and interpret data that might indicate specific areas where such tests can be useful for clinical management of cases, epidemiologic understanding, and/or infection control.
  - To this date, the ability of antibody tests to predict if individuals are immune to reinfection with COVID-19 is not known.

Advice on the use of point-of-care immunodiagnostic tests for COVID-19. [cited 2020 Apr 15]. Available from: https://www.who.int/news-room/commentaries/detail/advice-on-the-use-of-point-of-care-immunodiagnostic-tests-for-covid-19

Article 1: Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019

Aim and methods

- 173 cases of COVID-19, Shenzhen Third People's Hospital, China between Jan 11 and Feb 9, 2020
- Median age: 48 y (IQR, 35-61)
- The dynamics of total antibody (Ab), IgM and IgG antibody against SARS-CoV-2 in serial blood samples (n=535) were investigated by ELISA

Results

- The seroconversion rate: Ab (93.1% (161/173)) , IgM (82.7% (143/173)) and IgG (64.7% (112/173)
- Seroconversion median time (days): Ab (11), IgM (12)and IgG (14)
- Antibody assays positive rate was <40% within 1-week since onset, and increased to 100.0% (Ab), 94.3% (IgM) and 79.8% (IgG) since day-15 after onset. RNA detectability decreased from 66.7% at day-7 to 45.5% during day 15-39.
- RNA+Ab tests significantly raised the sensitivity (99.4%), even in early phase of 1-week since onset
- Antibody was detectable in patients with undetectable RNA in their respiratory tract samples

Discussion

- The antibody testing might play vital roles in the following settings
  - Suspected patients at the initial visit or clinically suspected patients without confirmed RNA test: the positive result of antibody increases the confidence to make a COVID-19 diagnosis
  - Healthy close contact in the quarantine period should be deemed as probable carrier if antibody positive. RNA should then be tested more frequently, and close contacts managed appropriately
- Limitation: duration of antibodies presence unknown

Conclusion: Antibody tests have important diagnosis value in addition to RNA tests

Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis. [cited 2020 Apr 13]; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa344/5812996

Article 2: Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19)

Aim:

- This study demonstrates the kinetics of antibody responses to SARS-CoV-2 in infected patients.
- The host humoral response against SARS-CoV-2 including IgA, IgM and IgG response using an ELISA based assay on the recombinant viral nucleocapsid protein
  - First cohort: 43 confirmed cases (CCs) (20 severe, 21 mild-moderate) and 58 probable cases (PCs) (5 severe, 53 mild-moderate), Wuhan hospitals, China
  - Second cohort: 39 hospitalized CCs (8 severe, 31 mild-moderate), Beijing hospital, China

Results

- Positivity rate: anti-SARS-CoV-2 IgM (85.4%), IgA (92.7%), IgG (77.9%)
- Median duration of IgM and IgA antibodies detection was 5 days (IQR 3-6), and for IgG was 14 days (IQR 10-18)
- The detection time of IgM, IgA, and IgG ranged from day 1 to 39 after onset
- The IgM-positive rate was 75.6% in CCs, and 93.1% PCs
- Positivity rate: IgM-ELISA+PCR increased to 98.6% , compared to 51.9% of single qPCR
- Efficiency by IgM ELISA is higher than that of PCR method after 5.5 days of onset

Discussion:

- The data show that IgM can provide a better sensitivity than qPCR-based method alone
- After a variable period of time, one expects the PCR result to become negative as people stop shedding virus. Presumably, IgG antibodies will remain positive.
- This would permit the use of serological tools to better understand the overall rate of infection in the community - including the rate of asymptomatic infections
- Identification of healthcare workers who have been infected in the past and might be less prone to becoming infected on the job
- The data also show its ability to detect subclinical infections effectively, a much-needed tool to stop the spread of infection

Conclusion: This can aid to the diagnosis of COVID-19, including subclinical cases

Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). Clin Infect Dis. [cited 2020 Apr 13]; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa310/5810754

Article 3: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)–Specific Antibody Responses in Coronavirus Disease 2019 Patients

Aim: Evaluate SARS-CoV-2–specific antibody responses to coronavirus proteins (spike protein (s) including the S1 subunit, nucleocapsid (N) and the receptor-binding domain (RBD) specific antibodies

- N and S proteins are the main immunogenic coronavirus proteins
- 246 serum samples from PCR-confirmed SARS-CoV-2 infections, other coronaviruses and other respiratory pathogenic infection (Netherlands, China, South Korea, France)
- Assay: Plaque reduction neutralization test (PRNT), ELISA (IgA and IgG), S1 protein microarray

Kinetics of antibody responses against SARS-CoV-2 after infection

- SARS-CoV-2–specific antibody responses in severe and mild cases seroconverted between days 13 and 21 after onset of disease
- Antibodies elicited against the SARS-CoV-2 S, S1 subunit, and RBD, but only 2/3 patients had detectable antibodies to the N-terminal
- S1 is more specific than S as an antigen for SARS-CoV-2 serologic diagnosis.

Cross-reactivity and performance of the assay

- Cross-reactivity between SARS-CoV-2 with the SARS-CoV S, S1 and RBD proteins.
- Lower cross reactivity between SARS-CoV-2 with MERS-CoV S and N protein, but not with the MERS-CoV S1 protein
- Cross reactivity between human coronavirus (HCoVOC43) and MERS-CoV S1 IgG
- S1 IgA-based ELISA showed higher sensitivity than IgG-based ELISA, the IgG ELISA showed higher specificity.
- The RBD and N protein ELISAs were more sensitive than S1 ELISA in detecting antibodies in mildly infected patients

Conclusion

- Detecting antibodies against 2 different antigens might be needed to confirm the findings and avoid false-negative results
- Assays described can be instrumental for detection of SARS-CoV-2–specific antibodies for diagnostic, sero-epidemiologic, and vaccine evaluation studies.

Article 4:Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis

Aim: Evaluate the clinical application of a developed rapid point of care test that can detect IgM and IgG antibodies simultaneously against SARS-CoV-2 virus in human blood within 15 minutes.

- A point-of-care lateral flow immunoassay (LFIA) test product was developed.
- The product was tested at 8 various hospitals and CDC testing laboratories in 6 different provinces in China.
- Sensitivity and specificity measure using different blood samples from participants.
- 525 study participants:
  397 positive confirmed SARS-CoV-2-infected patients,
  128 non- SARS-CoV-2-infected patients (negative)

IgM-IgG combined assay can be used for the rapid screening of SARS-CoV-2 carriers, symptomatic or asymptomatic, in hospitals, clinics, and test laboratories.

Performance of the SARS-CoV-2 IgG-IgM combined antibody test kit

- Higher sensibility of IgG-IgM combined antibody test than individual IgG or IgM antibody test
  - Sensitivity: 88.66% (352/397)
  - Specificity: 90.63% (12/128)
  - 64.48% (256/397) had both IgM and IgG positive compare to IgM only (72/397), IgG only (24/397)
- 94.83% (55/58) positive rate obtained when evaluated in 58 COVID-19 patients in Wuhan
- 100% consistency in the results among different blood samples (fingerstick, serum, plasma)

Limitations

- Possible cross-reactivity with other coronaviruses and flu viruses were not studied
- The change level of antibody was not compared in the different stages of SARS-CoV-2 infection.

Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, et al. Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis. J Med Virol. 2020 Feb 27; doi: 10.1002/jmv.25727.

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1. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis. [cited 2020 Apr 13]; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa344/5812996

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3. Okba NMA, Müller MA, Li W, Wang C, GeurtsvanKessel CH, Corman VM, et al. Severe acute respiratory syndrome coronavirus 2−specific antibody responses in coronavirus disease 2019 patients. Emerg Infect Dis. 2020 Jul [cited 2020 Apr 13]. https://doi.org/10.3201/eid2607.200841

4. Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, et al. Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis. J Med Virol. 2020 Feb 27; doi: 10.1002/jmv.25727.

This summary was prepared by Charles Manyelo and Bih Chendi (PhD candidates in molecular biology) as part of the daily brief to the TBH ICU Team (20 April 2020)