고려대학교의료원
KOREA UNIVERSITY MEDICINE

코로나바이러스감염증-19 (COVID-19) 인체면역반응

조 윤정
고려대학교 의과대학
고려대학교병원 진단검사의학과

ENABLING
FUTURE MEDICINE

Contents

- Naming COVID-19 and SARS-CoV-2
- Host immune perspectives: focused on humoral immunity
  - Introduction
  - Literature review
  - Public concern
- Why SARS-CoV-2 antibody test?

고려대학교의료원
KOREA UNIVERSITY MEDICINE

CORONAVIRUSES

Coronavirus Disease-19 (COVID-19)

- 병명: 코로나바이러스감염증-19 (코비드-19)
- 바이러스: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 사스 코브-2
- Viruses are named based on their genetic structure to facilitate the development of diagnostic tests, vaccines and medicines. Virologists and the wider scientific community do this work, so viruses are named by the International Committee on Taxonomy of Viruses (ICTV)
- Diseases are named to enable discussion on disease prevention, spread, transmissibility, severity and treatment. Human disease preparedness and response is WHO's role, so diseases are officially named by WHO in the International Classification of Diseases (ICD)

Coronavirus Disease-19 (COVID-19)

- ICTV announced “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)” as the name of the new virus on 11 February 2020. This name was chosen because the virus is genetically related to the coronavirus responsible for the SARS outbreak of 2003. While related, the two viruses are different.

- WHO announced “COVID-19” as the name of this new disease on 11 February 2020, following guidelines previously developed with the World Organization for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO).

SARS-CoV-2

- Positive-sense single-stranded RNA virus
  - Viral genomes act as mRNA
- 1 Segment, 30kb
  - Bat coronavirus (BatCoV RaTG13) 96.2% homology on genome level
  - 50% with MERS-CoV
  - 75% homology with SARS-CoV on S protein level
- Genome replication occurs in cytoplasm
  - RNA-dependent RNA polymerase(RdRp)
  - Error prone nature d/t minimal proofreading activities of RdRp
    - 3x higher error rate than DNA-dependent DNA polymerase(DdDp)
  - Can evolve up to 1 million times faster than DNA-based organisms
    - Rapid escape of the virus from neutralizing antibody
  - Nonstructural protein nsp14 functions as an RNA exonuclease (proofreading)

고려대학교의료원
KOREA UNIVERSITY MEDICINE

FROM HOST'S IMMUNE PERSPECTIVES

INTRODUCTION

Innate immunity

- Apoptosis (programmed cell suicide that limits the spread of infection)
- The induction and action of **interferons** (inducible cytokines that render cells resistant to infection by inducing a multifaceted antiviral state)
- Pathogen-recognition receptors (PRPs) recognize pathogen-associated molecular patterns (PAMPS)
  - Toll-like receptors (TLRs) on membrane
  - Retinoic acid inducible gene (RIG)-like receptors (RLRs) in cytoplasm

From hosts' specific immunity perspective

- Structural proteins are incorporated into virus particles
- Non-structural proteins are found only in infected cells
- Antibodies recognize viral Antigens
  - On virions & virus-infected cells
  - As soluble molecules produced by virally infected cells
  - As breakdown products from virions and infected cells
- Functionally active or inert antibodies
  - Active Abs reactive with viral antigens presented on virions/virally infected cells: minority
  - Inert Abs directed to non-surface viral antigens: majority

Nature of B cell receptor (BCR), antibody

- 6 CDRs: 3 from heavy chain, 3 from light chain
  - CDRH3
- Footprint (antibody contact area of antigen): 400~1,000 A
- Neutralization of free virus particles: the loss of infectivity that ensues when antibody molecules bind to a virus particle usually without the involvement of any other agency
  - Affinity for antigen on the virion surface (occupancy model)
  - Precise epitopes
  - Surface accessible epitopes

Antibodies

- Neutralizing antibody on virus surface
  - Neutralizing antibodies (at high titer)
  - Complement-medicated lysis and phagocytosis
- Other functions of antibodies
  - Fc-mediated cell lysis or clearance
  - Cell signaling mediated inhibition of viral replication
  - Steric obstruction leading to inhibition of virus release & cell-cell transmission

Coronaviruses receptors

- Sialic acid for human coronavirus 229E, OC43, NL63, HKU1
- Dipeptidyl peptidase 4 (DPP4) for MERS-CoV

- **Angiotensin converting enzyme 2 (ACE2)** for SARS-CoV & SARS-CoV-2
  - abundantly present in humans in the epithelia of the lung and small intestine
  - in vascular endothelium

  - Spike protein, **receptor binding domain (RBD)** of SARS-CoV-2

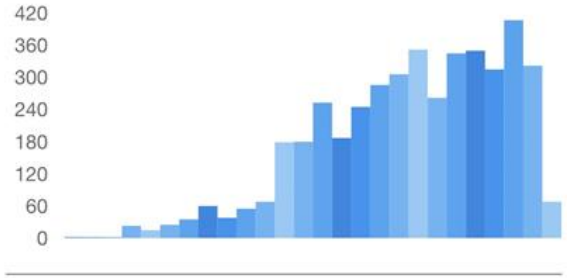
고려대학교의료원
KOREA UNIVERSITY MEDICINE

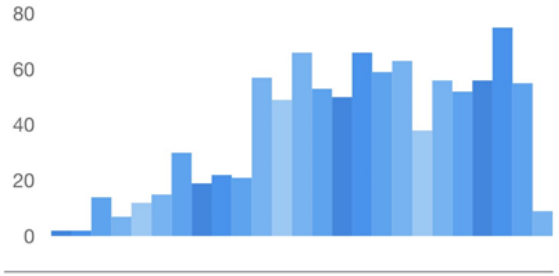
FROM HOST'S IMMUNE PERSPECTIVES

ORIGINAL ARTICLES

LitCovid, Diagnosis 4,382 (29,313) as of July 6

WEEKLY PUBLICATIONS





WORLD MAP

68 from 6 July, 2020
9 from China

A pneumonia outbreak associated with a new coronavirus of probable bat origin

https://doi.org/10.1038/s41586-020-2012-7

Received: 20 January 2020

Accepted: 29 January 2020

Published online: 3 February 2020

Open access

Check for updates

Peng Zhou[1,5], Xing-Lou Yang[1,5], Xian-Guang Wang[2,5], Ben Hu[1], Lei Zhang[1], Wei Zhang[1], Hao-Rui Si[1,3], Yan Zhu[1], Bei Li[1], Chao-Lin Huang[2], Hui-Dong Chen[2], Jing Chen[1,3], Yun Luo[1,3], Hua Guo[1,3], Ren-Di Jiang[1,3], Mei-Qin Liu[1,3], Ying Chen[1,3], Xu-Rui Shen[1,3], Xi Wang[1,3], Xiao-Shuang Zheng[1,3], Kai Zhao[1,3], Quan-Jiao Chen[1], Fei Deng[1], Lin-Lin Liu[4], Bing Yan[1], Fa-Xian Zhan[4], Yan-Yi Wang[1], Geng-Fu Xiao[1] & Zheng-Li Shi[1]✉

Since the outbreak of severe acute respiratory syndrome (SARS) 18 years ago, a large number of SARS-related coronaviruses (SARSr-CoVs) have been discovered in their natural reservoir host, bats[1–4]. Previous studies have shown that some bat SARSr-CoVs have the potential to infect humans[5–7]. Here we report the identification and characterization of a new coronavirus (2019-nCoV), which caused an epidemic of acute respiratory syndrome in humans in Wuhan, China. The epidemic, which started on 12 December 2019, had caused 2,794 laboratory-confirmed infections including 80 deaths by 26 January 2020. Full-length genome sequences were obtained from five patients at an early stage of the outbreak. The sequences are almost identical and share 79.6% sequence identity to SARS-CoV. Furthermore, we show that 2019-nCoV is 96% identical at the whole-genome level to a bat coronavirus. Pairwise protein sequence analysis of seven conserved non-structural proteins domains show that this virus belongs to the species of *SARSr-CoV*. In addition, 2019-nCoV virus isolated from the bronchoalveolar lavage fluid of a critically ill patient could be neutralized by sera from several patients. Notably, we confirmed that 2019-nCoV uses the same cell entry receptor—angiotensin converting enzyme II (ACE2)—as SARS-CoV.

고려대학교의료원
KOREA UNIVERSITY MEDICINE

Patient information and diagnosis history

Patient No.	Gender	Age	Date of Onset	Date of Admission	Symptoms When Admitted	Current Status (2020.01.13)	Diagnosis history
ICU-01*	Male	62	2019.12.12	2019.12.27	fever	recover, discharged	negative
ICU-04	Male	32	2019.12.19	2019.12.29	fever, cough, dyspnea	fever, intermittent cough	negative
ICU-05	Male	40	2019.12.17	2019.12.27	fever (38 °C), expectoration, malaise, dyspnea	fever, malaise, intermittent cough	AdV (IgM)
ICU-06	Female	49	2019.12.23	2019.12.27	fever (37.9 °C), palpitation	fever, malaise, cough	Coronavirus (nt)
ICU-08	Female	52	2019.12.22	2019.12.29	fever (38.5 °C), expectoration, malaise, dyspnea	recover, discharged	Streptococcus pneumoniae (nt)
ICU-09	Male	40	2019.12.22	2019.12.28	fever (38.5 °C), expectoration	fever (38.5 °C), malaise, expectoration, dizziness	negative
ICU-10	Male	56	2019.12.20	2019.12.20	fever, dyspnea, chest tightness	fever, malaise, cough, dyspnea	negative

Note, some records are missing. All patients are sellers or deliverymen at the seafood market except ICU-01, whose contact history is unclear. All patients were admitted to intensive care unit (ICU) during the first investigation and were now in stable condition. Blood IgM tests have been performed for the following respiratory pathogens for all patients: *Legionella pneumophilia*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, respiratory syncytial virus, adenovirus, *Rickettsia*, influenza A virus, influenza B virus and parainfluenza virus.

*This patient reported fever on 12 December 2019 and then recovered without medical treatment. He came back to the hospital on 27 December 2019 with a fever. His wife was also ill and admitted to the hospital. Both individuals recovered.

Laboratory results

		First sampling-2019.12.30			Second sampling-2020.01.10			
Patient No.	Test No.	BALF	Oral Swab	Blood (Ab)	Oral Swab	Anal Swab	Blood (PCR)	Blood (Ab)
ICU-01	WIV01	-	Ct=32.0	NA	NA	NA	NA	NA
ICU-04	WIV02[#]	Ct=17.6	Ct=26.6	NA	-	-	-	+
ICU-05	WIV03	Ct=27.0	Ct=31.9	NA	-	-	-	+
ICU-06	WIV04[#*]	Ct=18.3	Ct=27.7	+	-	-	-	+
ICU-08	WIV05[#]	Ct=24.1	-	NA	NA	NA	NA	NA
ICU-09	WIV06[#]	Ct=21.6	Ct=29.4	NA	-	-	-	+
ICU-10	WIV07[#]	Ct=25.7	Ct=24.0	NA	-	-	-	+

Samples from two patients (ICU-01 and ICU-08) were not available during the second investigation. They had been discharged from the hospital. We did a serial test for patient ICU-06 on the following dates: 30 December 2019, 31 December 2019, 1 January 2020 and 10 January 2020, corresponding to 7, 8, 9 and 18 days after disease onset (23 December 2019). Molecular and serological (IgM and IgG) virus-detection results for 2019-nCoV are shown. NA, not available.

*Virus isolated.

#A full-length genome was obtained.

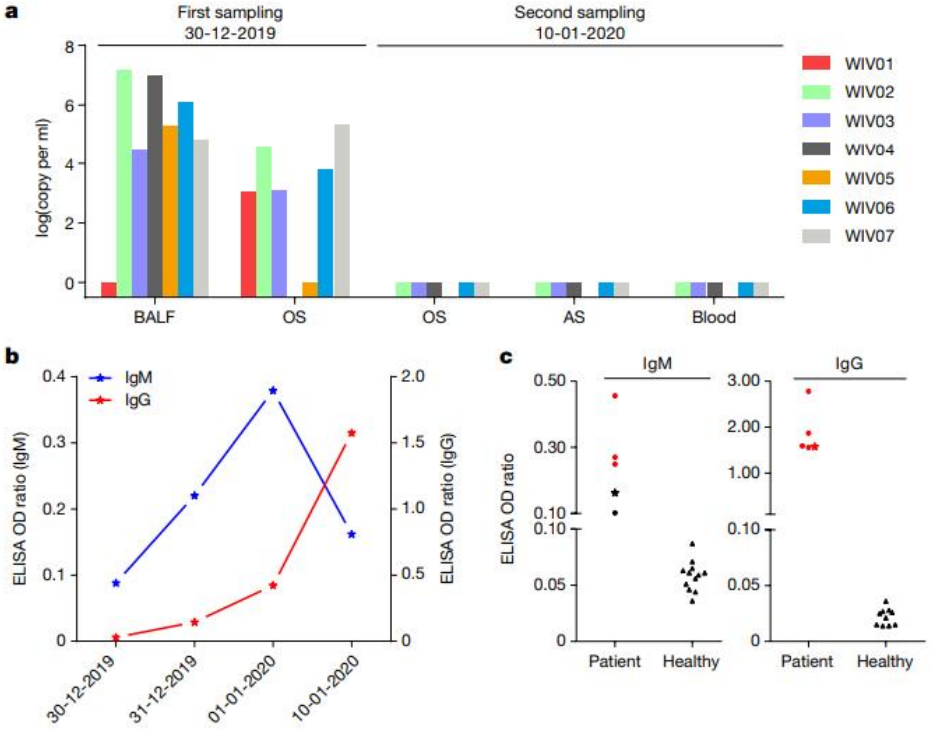


Fig. 2 | Molecular and serological investigation of patient samples. **a**, Molecular detection of 2019-nCoV in seven patients. Patient information can be found in Extended Data Tables 1, 2. Detection methods are described in the Methods. AS, anal swab; OS, oral swab. **b**, Dynamics of 2019-nCoV antibody levels in one patient who showed signs of disease on 23 December 2019 (ICU-06). OD ratio, optical density at 450–630 nm. The right and left *y* axes indicate ELISA OD ratios for IgM and IgG, respectively. **c**, Serological test of 2019-nCoV antibodies in five patients (Extended Data Table 2). The asterisk indicates data collected from patient ICU-06 on 10 January 2020. **b**, **c**, The cut-off was to 0.2 for the IgM analysis and to 0.3 for the IgG analysis, according to the levels of healthy controls.

Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine

Wanbo Tai[1], Lei He[2], Xiujuan Zhang[1], Jing Pu[1,3], Denis Voronin[1], Shibo Jiang[1,3], Yusen Zhou[2] and Lanying Du[1]

The outbreak of Coronavirus Disease 2019 (COVID-19) has posed a serious threat to global public health, calling for the development of safe and effective prophylactics and therapeutics against infection of its causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as 2019 novel coronavirus (2019-nCoV). The CoV spike (S) protein plays the most important roles in viral attachment, fusion and entry, and serves as a target for development of antibodies, entry inhibitors and vaccines. Here, we identified the receptor-binding domain (RBD) in SARS-CoV-2 S protein and found that the RBD protein bound strongly to human and bat angiotensin-converting enzyme 2 (ACE2) receptors. SARS-CoV-2 RBD exhibited significantly higher binding affinity to ACE2 receptor than SARS-CoV RBD and could block the binding and, hence, attachment of SARS-CoV-2 RBD and SARS-CoV RBD to ACE2-expressing cells, thus inhibiting their infection to host cells. SARS-CoV RBD-specific antibodies could cross-react with SARS-CoV-2 RBD protein, and SARS-CoV RBD-induced antisera could cross-neutralize SARS-CoV-2, suggesting the potential to develop SARS-CoV RBD-based vaccines for prevention of SARS-CoV-2 and SARS-CoV infection.

Keywords: 2019 novel coronavirus; SARS-CoV-2; spike protein; receptor-binding domain; viral inhibitor; cross-neutralization

Cellular & Molecular Immunology (2020) 17:613–620; https://doi.org/10.1038/s41423-020-0400-4

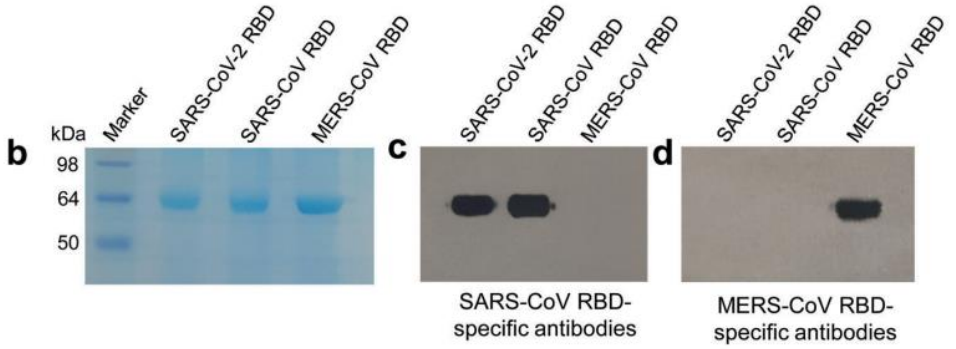
a

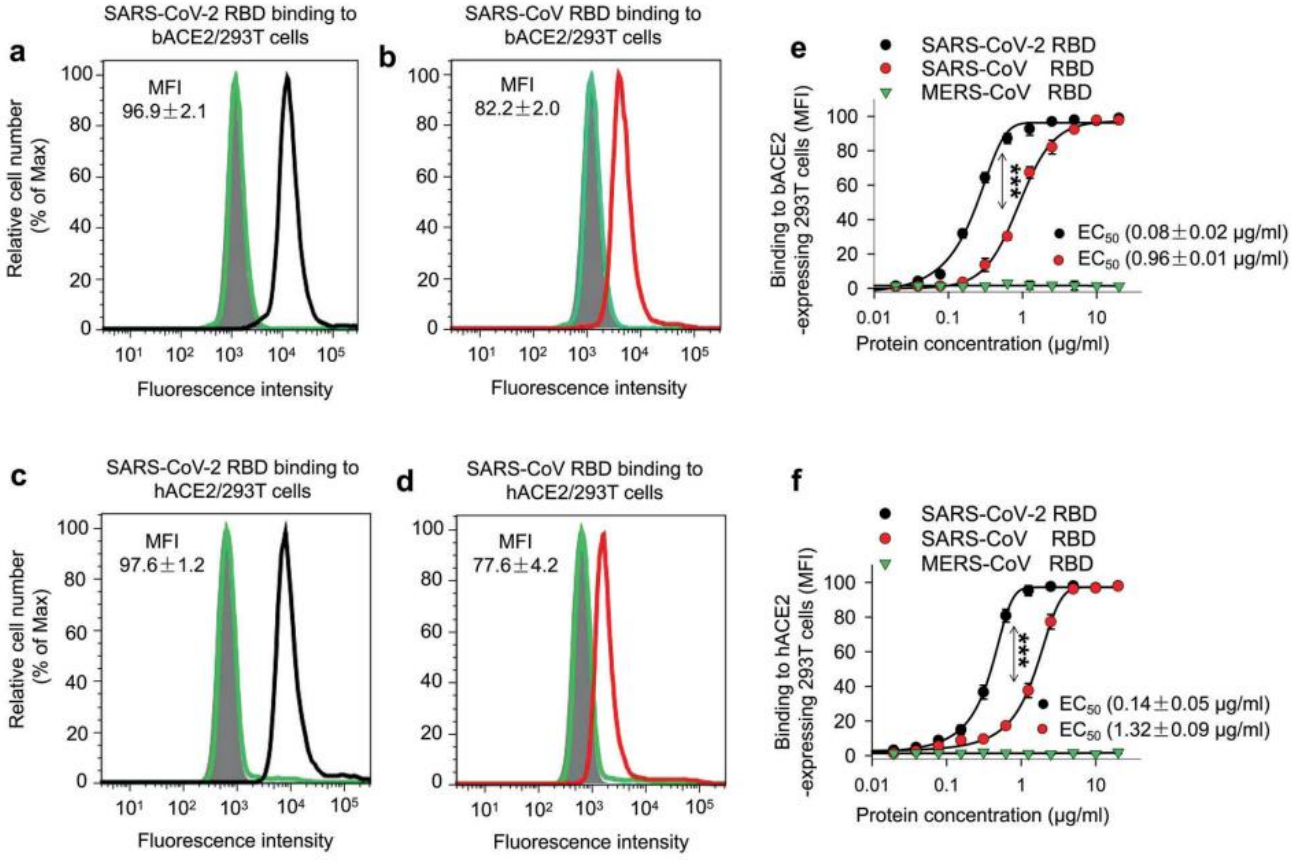
```
SARS-CoV-2  331   -NITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLND   389
SARS-CoV    318   -NITNLCPFGEVFNATKFPSVYAWERKKISNCVADYSVLYNSTFFSTFKCYGVSATKLND   376
MERS-CoV    377   QAEGVECDFSPLLSG-TPPQVYNFKRLVFTNCNYNLTKLLSLFSVNDFTCSQISPAAIAS   435
                        *.*::..    . .**:  *::  **: :   *   .. *.* *:* : : .

SARS-CoV-2  390   LCFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNY   449
SARS-CoV    377   LCFSNVYADSFVVKGDDVRQIAPGQTGVIADYNYKLPDDFMGCVLAWNTRNIDATSTGNY   436
MERS-CoV    436   NCYSSLILDYFSYPLSMKSDLSVSSAGPISQFNYKQSFSNPTCLILATVPHNLTTITKPL   495
                   *::.:  * *    .   ::: ..:* *:::***   .   *::  .  :  :.

SARS-CoV-2  450   NYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFP-----------LQSYGFQ   498
SARS-CoV    437   NYKYRYLRHGKLRPFERDISNVPFSPDGKPCT-PPALNCYWP-----------LNDYGFY   484
MERS-CoV    496   KYSYINKCSRLLSDDRTEVPQLVNANQYSPCVSIVPS-TVWEDGDYYRKQLSPLEGGGWL   554
                  :* *       *   . ::         .**        :           *:. *:

SARS-CoV-2  499   PTNGVGYQPYRVVVLSFELLHAPAT----V----                            524
SARS-CoV    485   TTTGIGYQPYRVVVLSFELLNAPAT----V----                            510
MERS-CoV    555   VASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKL                            588
                   :.*      . : :.* :    .*    *
```




a
SARS-CoV-2 RBD binding to bACE2/293T cells
MFI
96.9±2.1
Relative cell number (% of Max)
Fluorescence intensity
b
SARS-CoV RBD binding to bACE2/293T cells
MFI
82.2±2.0
Fluorescence intensity
c
SARS-CoV-2 RBD binding to hACE2/293T cells
MFI
97.6±1.2
Relative cell number (% of Max)
Fluorescence intensity
d
SARS-CoV RBD binding to hACE2/293T cells
MFI
77.6±4.2
Fluorescence intensity
e
SARS-CoV-2 RBD
SARS-CoV RBD
MERS-CoV RBD
Binding to bACE2 -expressing 293T cells (MFI)
***
EC50 (0.08±0.02 μg/ml)
EC50 (0.96±0.01 μg/ml)
Protein concentration (μg/ml)
f
SARS-CoV-2 RBD
SARS-CoV RBD
MERS-CoV RBD
Binding to hACE2 -expressing 293T cells (MFI)
***
EC50 (0.14±0.05 μg/ml)
EC50 (1.32±0.09 μg/ml)
Protein concentration (μg/ml)

Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study

Kelvin Kai-Wang To, Owen Tak-Yin Tsang*, Wai-Shing Leung, Anthony Raymond Tam, Tak-Chiu Wu, David Christopher Lung, Cyril Chik-Yan Yip, Jian-Piao Cai, Jacky Man-Chun Chan, Thomas Shiu-Hong Chik, Daphne Pui-Ling Lau, Chris Yau-Chung Choi, Lin-Lei Chen, Wan-Mui Chan, Kwok-Hung Chan, Jonathan Daniel Ip, Anthony Chin-Ki Ng, Rosana Wing-Shan Poon, Cui-Ting Luo, Vincent Chi-Chung Cheng, Jasper Fuk-Woo Chan, Ivan Fan-Ngai Hung, Zhiwei Chen, Honglin Chen, Kwok-Yung Yuen*

Summary

Background Coronavirus disease 2019 (COVID-19) causes severe community and nosocomial outbreaks. Comprehensive data for serial respiratory viral load and serum antibody responses from patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are not yet available. Nasopharyngeal and throat swabs are usually obtained for serial viral load monitoring of respiratory infections but gathering these specimens can cause discomfort for patients and put health-care workers at risk. We aimed to ascertain the serial respiratory viral load of SARS-CoV-2 in posterior oropharyngeal (deep throat) saliva samples from patients with COVID-19, and serum antibody responses.

Lancet Infect Dis 2020; 20: 565–74

Published Online March 23, 2020 https://doi.org/10.1016/S1473-3099(20)30196-1

See Comment page 515

*Contributed equally

	Severe disease (n=10)	Mild disease (n=13)	p value
(Continued from previous page)			
Viral load in respiratory tract specimens			
Initial viral load, log_{10} copies per mL (IQR)	6·17 (4·18–7·13)	5·11 (3·91–7·56)	0·56
Peak viral load, log_{10} copies per mL (IQR)	6·91 (4·27–7·40)	5·29 (3·91–7·56)	0·52
Viral RNA detection			
≥20 days in saliva*	4 (50%)	3 (23%)	0·35
Blood	3 (30%)	2 (15%)	0·62
Rectal swab†	3 (38%)	1 (14%)	0·57
Urine‡	0 (0%)	0 (0%)	..

Data are n (%) or median (range), unless otherwise stated. For statistical analyses, the Mann-Whitney *U* test was done for continuous variables and Fisher's exact test was done for categorical variables. *For severe disease, the total number of patients was eight (two patients died <20 days after symptom onset). †For severe disease, samples were available for eight patients; for mild disease, samples were available for seven patients. ‡For severe and mild disease, samples were available for nine patients in each group.

Table: **Patients' characteristics, by severity of disease**

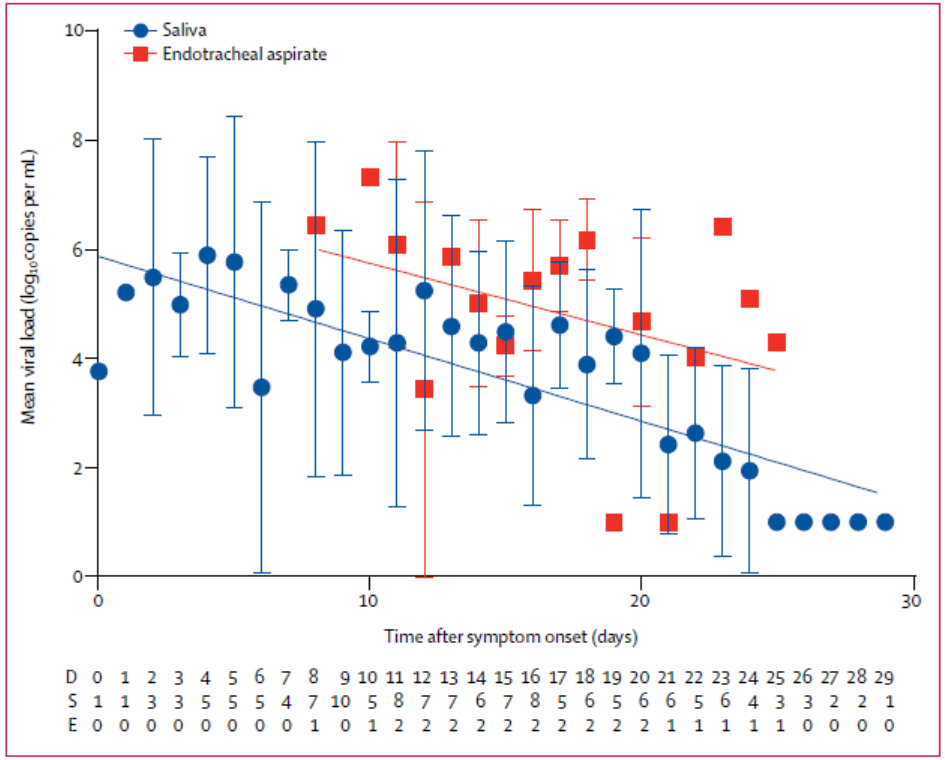
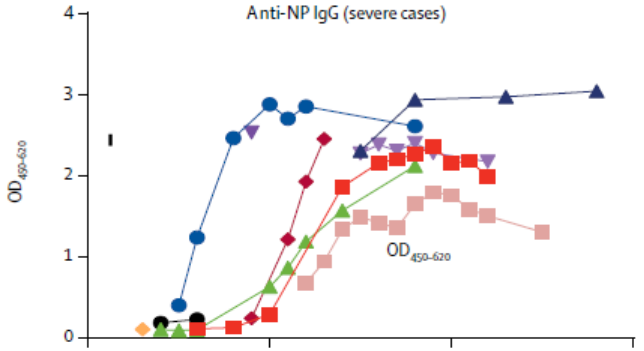
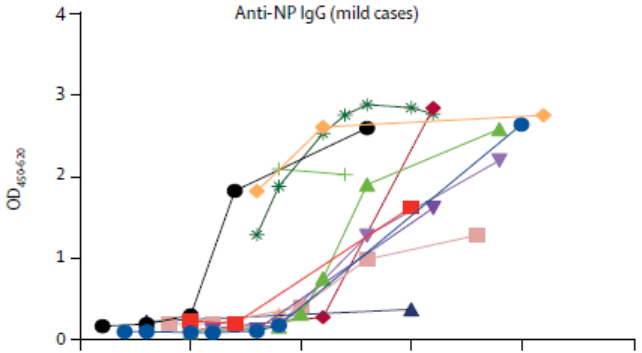
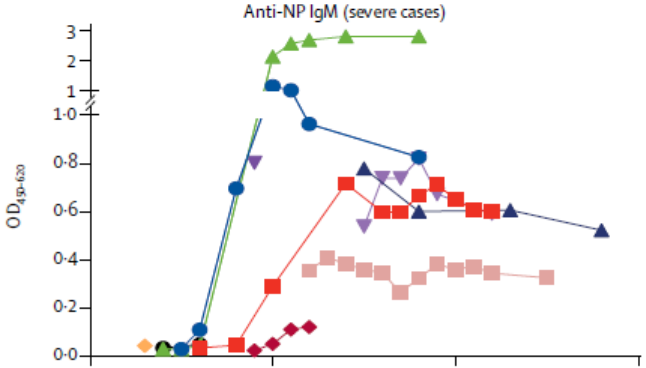
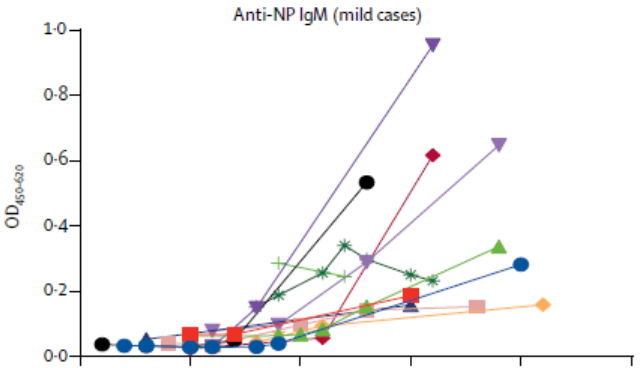


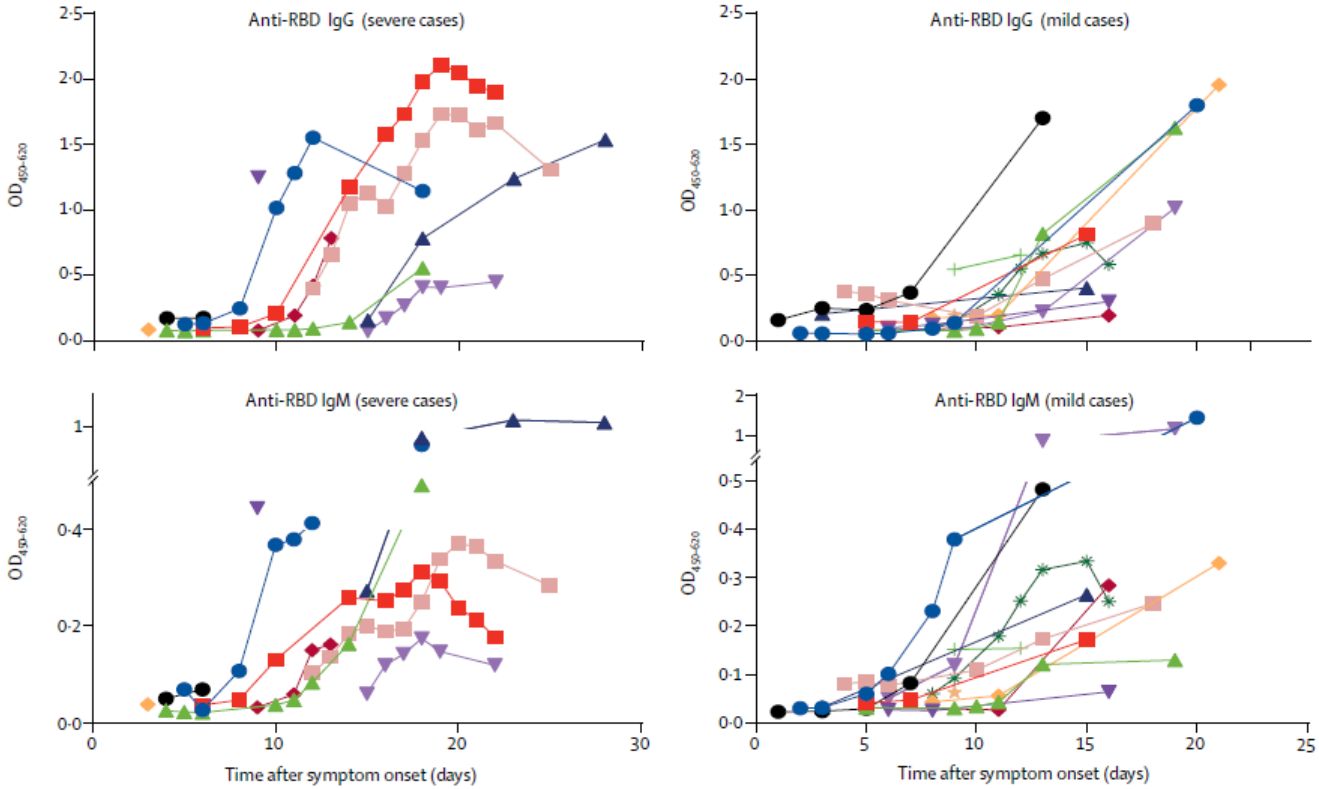
Figure 2: **Temporal profile of serial viral load from all patients (n=23)**
Most viral load data are from posterior oropharyngeal saliva samples, except for three patients who were intubated, in whom viral load data from endotracheal aspirates are shown separately. Datapoints denote the mean; error bars indicate SD; slope represents best fit line. The number of patients who provided a sample on each day is shown in the table below the plot. D=days after symptom onset. S=saliva. E=endotracheal aspirate.


Anti-NP IgG (severe cases)
OD450-620
OD450-620


Anti-NP IgG (mild cases)
OD450-620


Anti-NP IgM (severe cases)
OD450-620


Anti-NP IgM (mild cases)
OD450-620


Anti-RBD IgG (severe cases)
Anti-RBD IgG (mild cases)
Anti-RBD IgM (severe cases)
Anti-RBD IgM (mild cases)
OD450-620
Time after symptom onset (days)

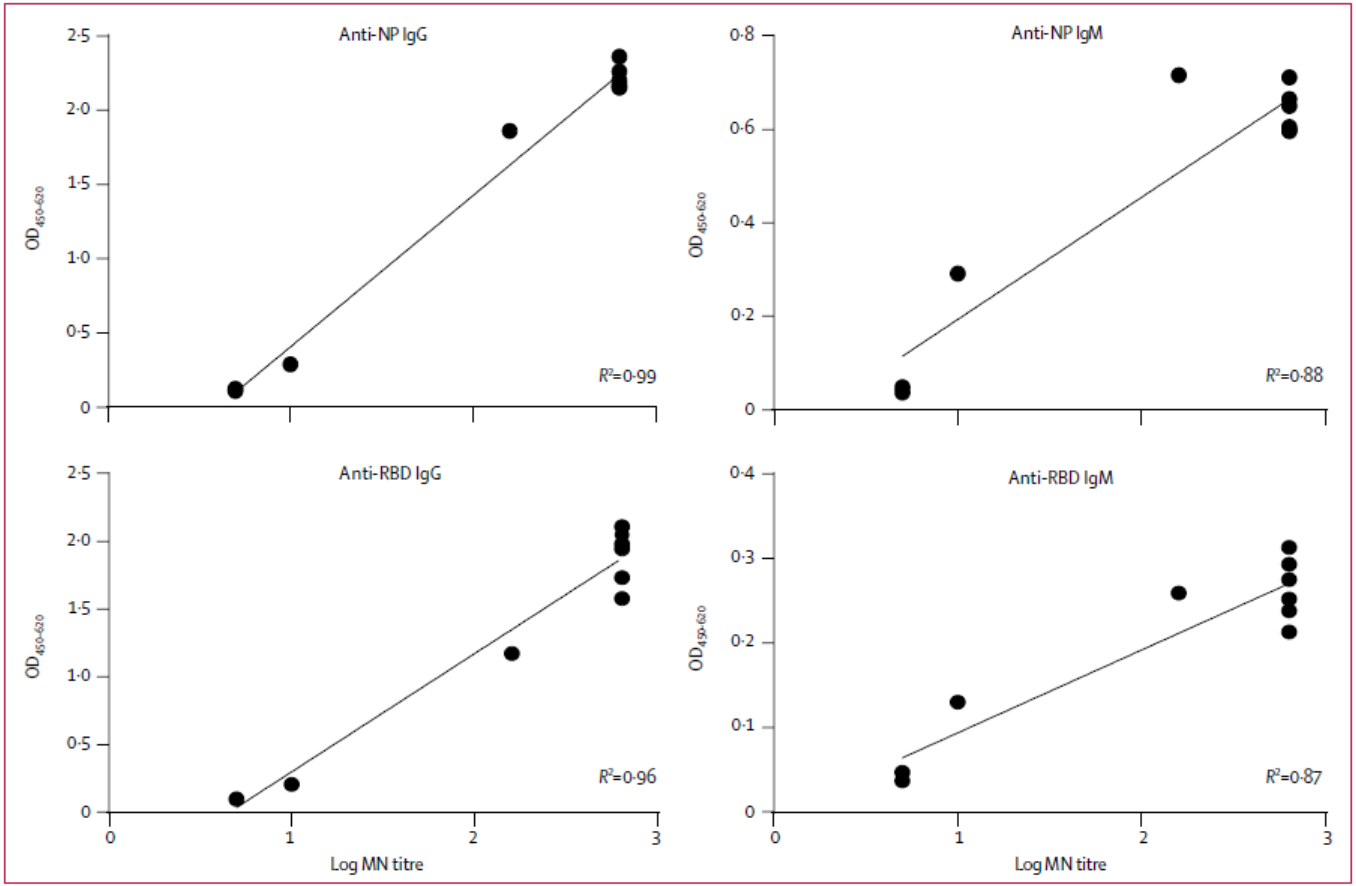


Figure 5: **Correlation between MN antibody titres and anti-NP or anti-RBD IgG or IgM**
$OD_{450-620}$=optical density at 450–620 nm. MN=microneutralisation. NP=nucleoprotein. RBD=receptor-binding domain.

Value and implications

- Salivary viral load was highest during the first week after symptom onset and subsequently declined with time
- EIA of IgG and IgM against internal viral nucleoprotein (NP) and surface spike protein receptor binding domain (RBD) showed correlation between antibody response and neutralizing antibody titer.
- Posterior oropharyngeal saliva specimens can be used for initial diagnosis and subsequent viral load monitoring of COVID-19.
- The early peaking of viral load has important implications for transmission of SARS-CoV-2 in the community and hospital settings.
- EIA of IgG and IgM against internal viral NP and surface spike protein RBD can be used for those with delayed presentation or retrospective diagnosis of mild cases.
- As the positive EIA antibody level correlates well with neutralizing antibody titer, further studies on its role in immunopathology or antiviral therapy are warranted.

nature medicine

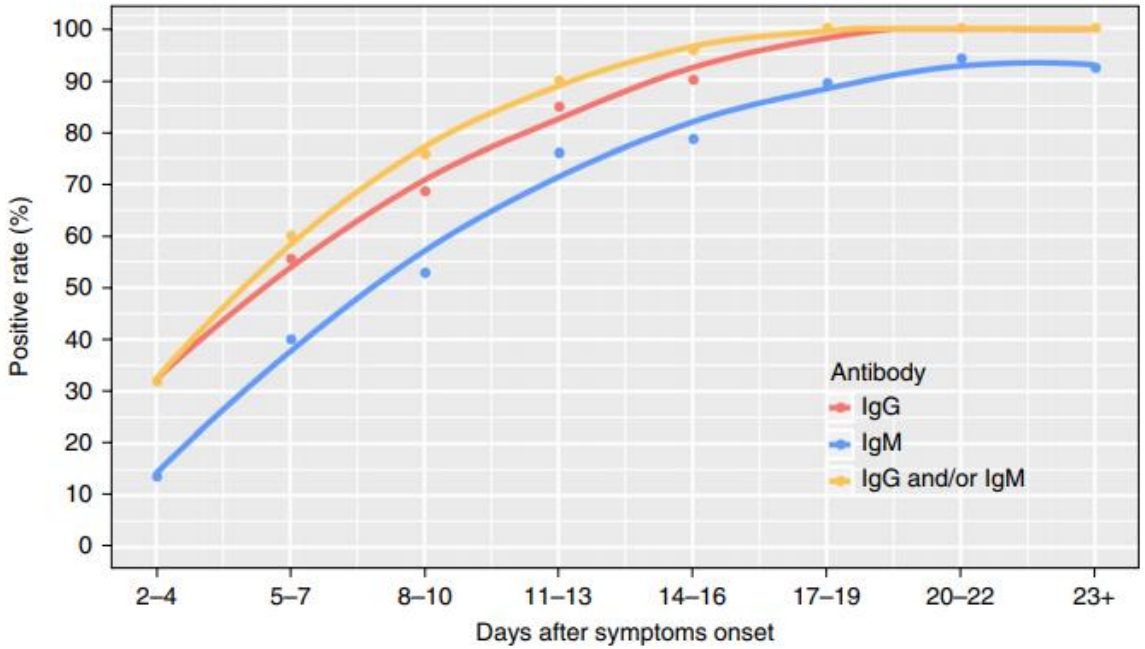
BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-020-0897-1

Antibody responses to SARS-CoV-2 in patients with COVID-19

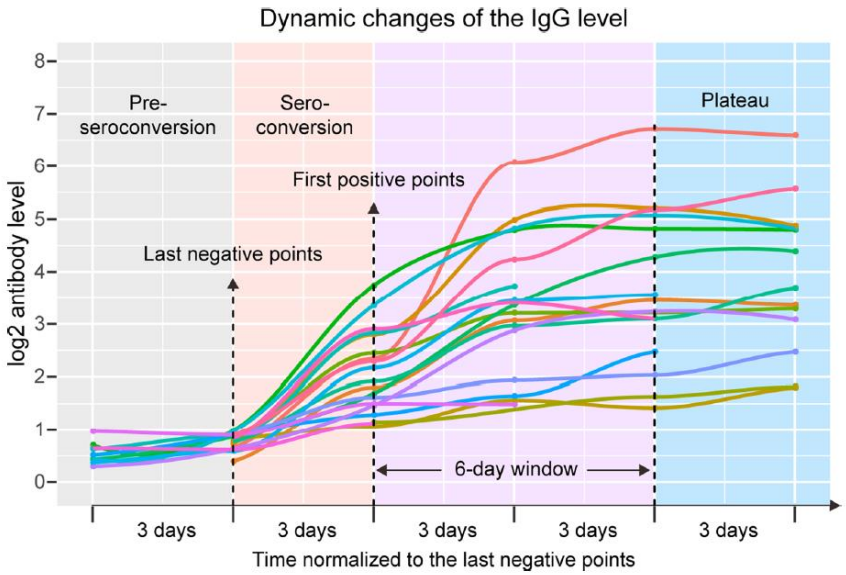
Quan-Xin Long[1,13], Bai-Zhong Liu[2,13], Hai-Jun Deng[1,13], Gui-Cheng Wu[3,4,13], Kun Deng[5,13], Yao-Kai Chen[6,13], Pu Liao[7], Jing-Fu Qiu[8], Yong Lin[1], Xue-Fei Cai[1], De-Qiang Wang[1], Yuan Hu[1], Ji-Hua Ren[1], Ni Tang[1], Yin-Yin Xu[2], Li-Hua Yu[2], Zhan Mo[2], Fang Gong[2], Xiao-Li Zhang[2], Wen-Guang Tian[2], Li Hu[2], Xian-Xiang Zhang[3,4], Jiang-Lin Xiang[3,4], Hong-Xin Du[3,4], Hua-Wen Liu[3,4], Chun-Hui Lang[3,4], Xiao-He Luo[3,4], Shao-Bo Wu[3,4], Xiao-Ping Cui[3,4], Zheng Zhou[3,4], Man-Man Zhu[5], Jing Wang[6], Cheng-Jun Xue[6], Xiao-Feng Li[6], Li Wang[6], Zhi-Jie Li[7], Kun Wang[7], Chang-Chun Niu[7], Qing-Jun Yang[7], Xiao-Jun Tang[8], Yong Zhang[8], Xia-Mao Liu[9], Jin-Jing Li[9], De-Chun Zhang[10], Fan Zhang[10], Ping Liu[11], Jun Yuan[1], Qin Li[12], Jie-Li Hu[1]✉, Juan Chen[1]✉ and Ai-Long Huang[1]✉

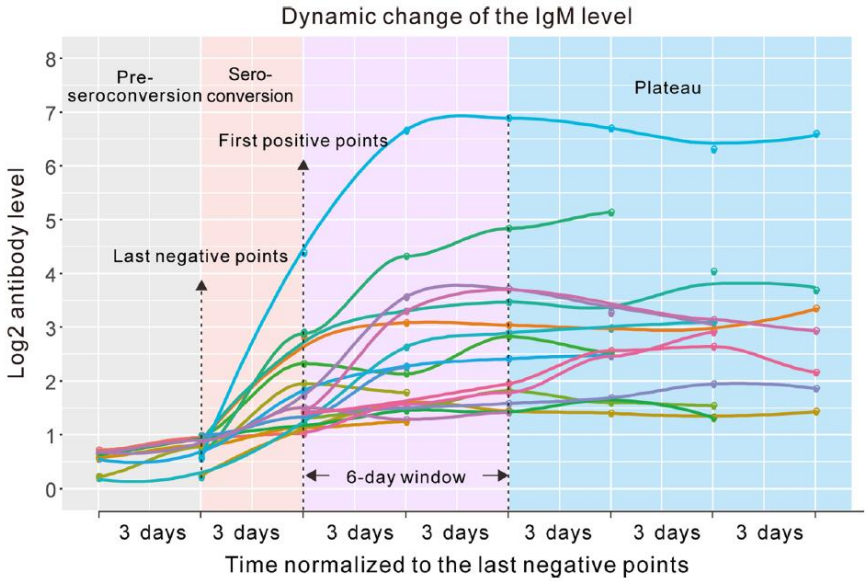
Positive rates of SARS-CoV-2-specific IgG/IgM in 363 serum samples from 262 patients



고려대학교의료원
KOREA UNIVERSITY MEDICINE

Dynamic changes of the SARS-CoV-2 specific Ig





nature medicine

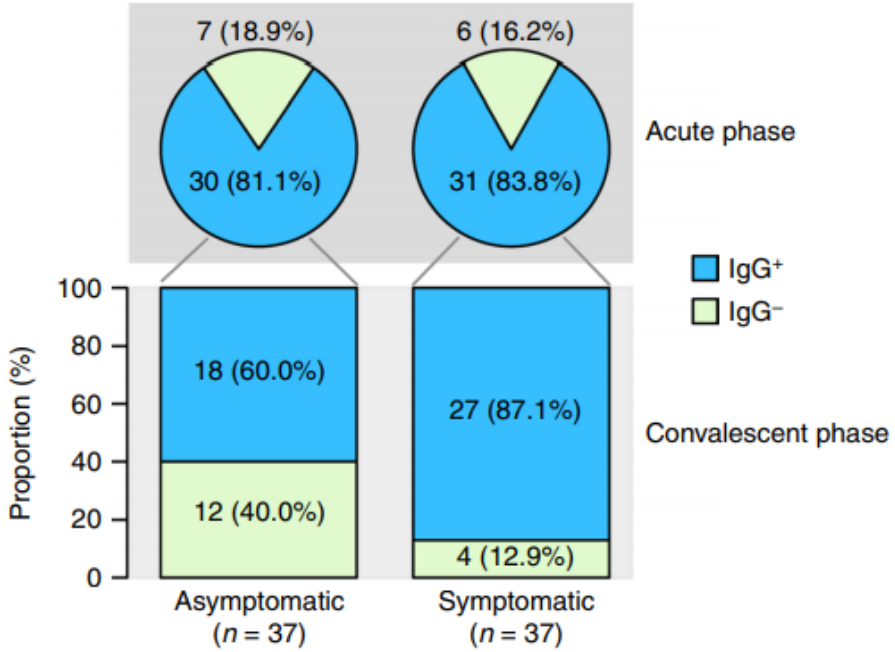
LETTERS

https://doi.org/10.1038/s41591-020-0965-6

Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections

Quan-Xin Long[1,8], Xiao-Jun Tang[2,8], Qiu-Lin Shi[2,8], Qin Li[3,8], Hai-Jun Deng[1,8], Jun Yuan[1], Jie-Li Hu[1], Wei Xu[2], Yong Zhang[2], Fa-Jin Lv[4], Kun Su[3], Fan Zhang[5], Jiang Gong[5], Bo Wu[6], Xia-Mao Liu[7], Jin-Jing Li[7], Jing-Fu Qiu[2]✉, Juan Chen[1]✉ and Ai-Long Huang[1]✉

IgG-positive proportions of patients with COVID-19 in the acute and convalescent phases



Asymptomatic individuals had a weaker immune response to SARS-CoV-2 infection

	Symptomatic pts	Asymptomatic pts
Viral shedding median duration	14 d	19 d (15 – 26d)
Virus-specific IgG level (S/CO) in acute phase	20.5	3.4
Reduction in IgG & NA during the early convalescent phase	96.8/62.2%	93.3/81.1%
Seronegative for IgG in the early convalescent phase	12.9%	40%
Level of 18 pro- & anti-inflammatory cytokines		Lower level

Implications

- 37 (20.8%) out of 178 laboratory-confirmed pts never developed any symptoms throughout the disease course
- Timely RT–PCR and serological testing should be used in conjunction, which would benefit accurate estimation of the asymptomatic proportion
  - Vary in their specificity and sensitivity
  - Confounded by previously existing antibodies to SARS-CoV, MERS-CoV or common cold coronaviruses

Disease control measures should be adjusted to account for probable substantial pre-symptomatic transmission

- 94 patients with laboratory-confirmed COVID-19
- modeled COVID-19 infectiousness profiles from a separate sample of 77 infector–infectee transmission pairs
- The highest viral load in throat swabs at the time of symptom onset
- Infectiousness peaked on or before symptom onset
- 44% (95% confidence interval, 25–69%) of secondary cases were infected during the index cases' pre-symptomatic stage, in settings with substantial household clustering, active case finding and quarantine outside the home.

TABLE 9.6 Humoral Response to Acute Viral Infection in Humans

Example	Virus family	Persistence of antibody
Systemic infections		
Chikungunya	*Alphaviridae*	30 yr
Rift Valley fever	*Bunyaviridae*	12 yr
Dengue	*Flaviviridae*	32 yr
Yellow fever	*Flaviviridae*	75 yr
Measles	*Paramyxoviridae*	65 yr
Mumps	*Paramyxoviridae*	12 yr
Polio	*Picornaviridae*	40 yr
Hepatitis A	*Picornaviridae*	25 yr
Smallpox	*Poxviridae*	40 yr
Vaccinia	*Poxviridae*	75 yr
Rubella	*Togaviridae*	14 yr
Mucosal infections		
Coronavirus	*Coronaviridae*	12 mo
Influenza	*Orthomyxoviridae*	30 mo
RSV	*Paramyxoviridae*	3 mo
Rotavirus	*Reoviridae*	12 mo

RSV, respiratory syncytial virus; yr, year; mo, month.

Modified from Slifka MK, Ahmed R. Long-term humoral immunity against viruses: revisiting the issue of plasma cell longevity. Trends Microbiol 1996;4:394–400.

Antibody Tests for Identification of Current and Past Infection With SARS-CoV-2

- 57 publications
  - 54 study cohorts with 15,976 samples
  - 8526 were from cases of SARS-CoV-2 infection
  - Asia (n = 38), Europe (n = 15), and the USA and China (n = 1)
- The combination of IgG/IgM had a sensitivity of
  - 30.1% (95% CI 21.4 to 40.7) for 1 to 7 days
  - 72.2% (95% CI 63.5 to 79.5) for 8 to 14 days
  - 91.4% (95% CI 87.0 to 94.4) for 15 to 21 days

Cochrane Database Syst Rev. 2020 Jun
doi: 10.1002/14651858.CD013652

Role of antibody tests and study design

- May still have a role complementing other testing
  - in individuals presenting later
  - when RT-PCR tests are negative, or are not done
- Likely to have a useful role for detecting previous SARS-CoV-2 infection if used 15 or more days after the onset of symptoms
- The duration of antibody rises is currently unknown; very little data beyond 35 days post-symptom onset
- **Must report data on sensitivity disaggregated by time since onset of symptoms**
- COVID-19-positive cases (RT-PCR-negative/positive) should be included in accordance with WHO and China National Health Commission of the People's Republic of China (CDC) case definitions

Cochrane Database Syst Rev. 2020 Jun
doi: 10.1002/14651858.CD013652

고려대학교의료원
KOREA UNIVERSITY MEDICINE

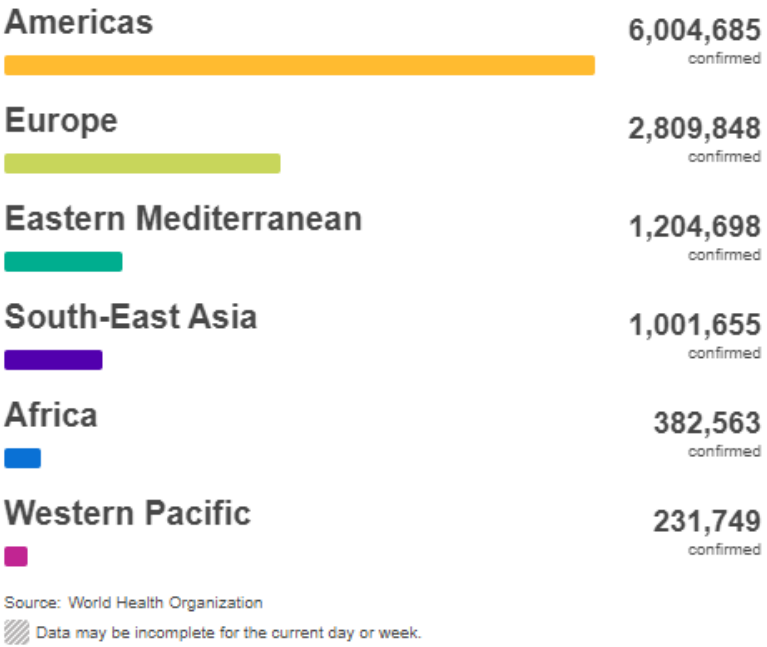
FROM HOST'S IMMUNE PERSPECTIVES

OUR UNDERSTANDING AS OF TODAY

PUBLIC HEALTH CONCERN

고려대학교의료원
KOREA UNIVERSITY MEDICINE

Situation by WHO region as of 8 July 2020



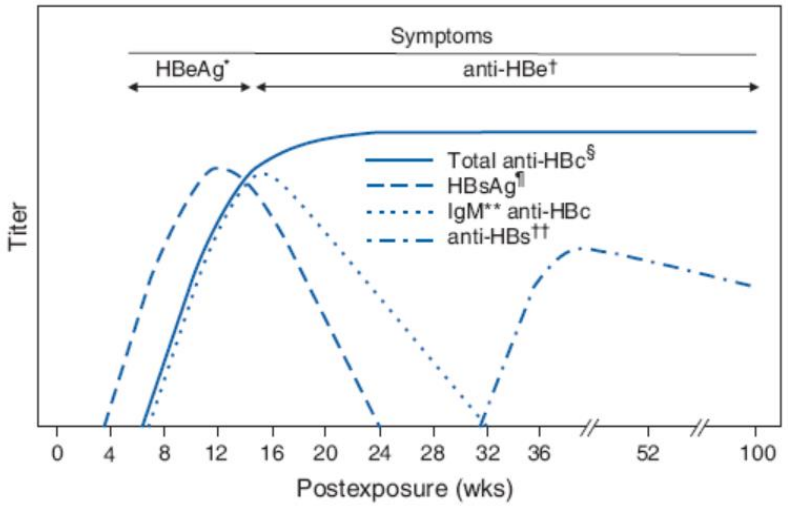
In **Republic of Korea**, from **Jan 19** to **6:58pm CEST, 8 July 2020**, there have been **13,244 confirmed cases** of COVID-19 with **285 deaths**.

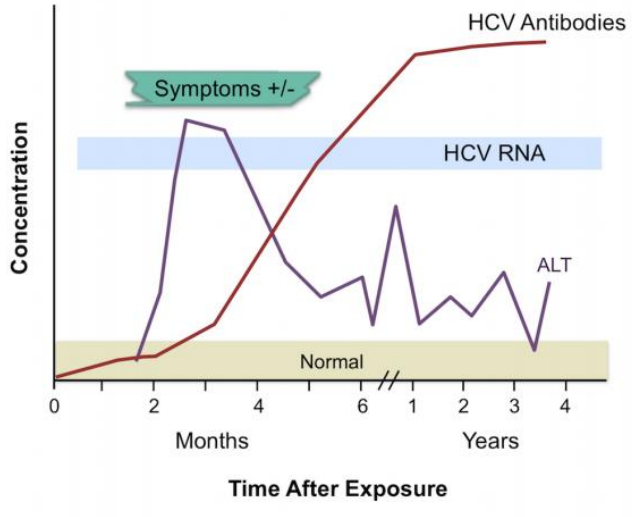
https://covid19.who.int/

Why SARS-CoV-2 specific antibodies important?

- First, serological assays allow us to study the immune response(s) to SARS-CoV-2 in a qualitative and quantitative manner
- Second, serosurveys are needed to determine the precise rate of infection in an affected area, which is an essential variable to accurately determine the infection fatality rate
- Third, serological assays will allow for the identification of individuals who mounted strong antibody responses and who could serve as donors for the generation of convalescent serum/plasma therapeutics
- Lastly, serological assays can help inform studies that aim to identify antibody responses that correlate with protection from SARS-CoV-2.

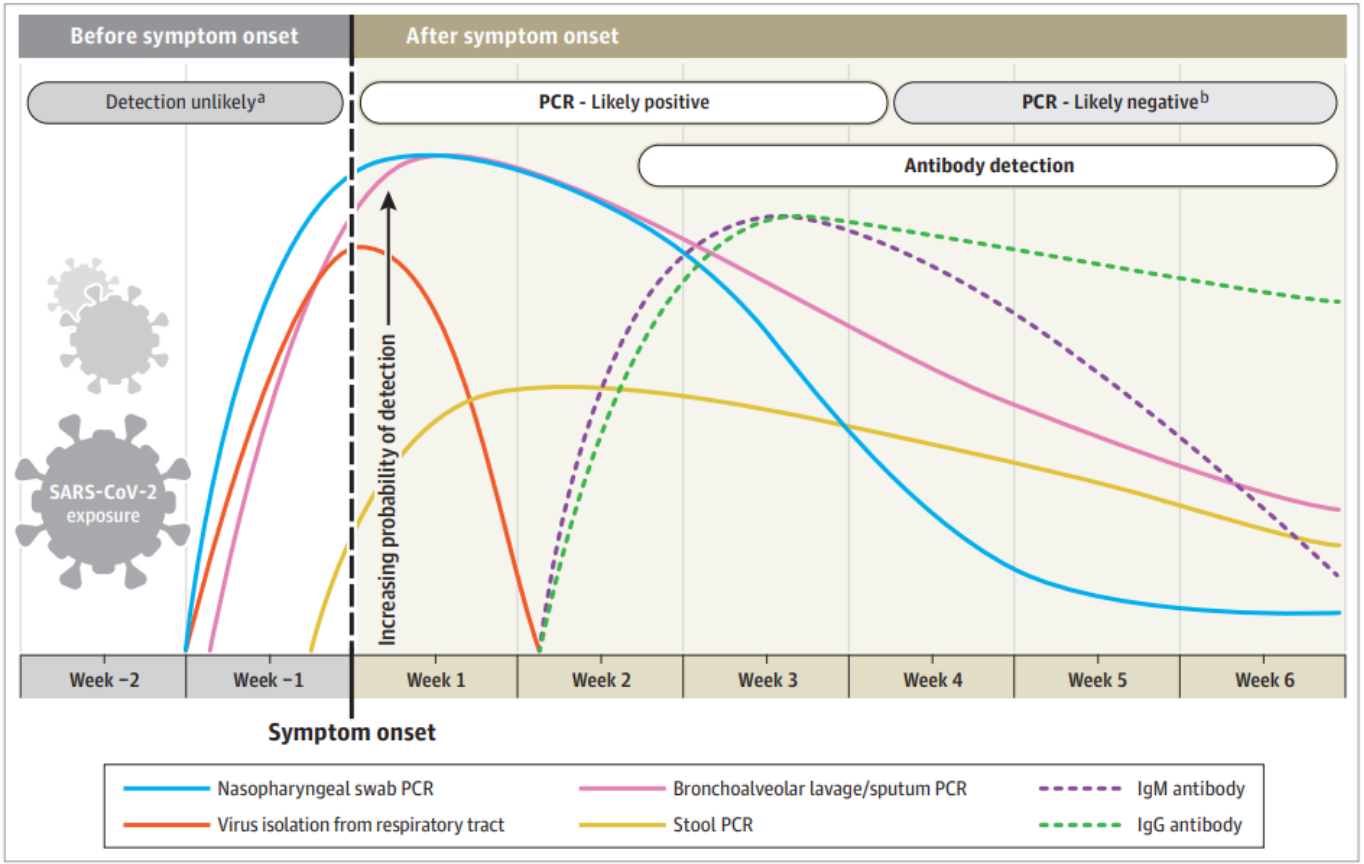
Laboratory markers for HBV & HCV infection





Centers for Disease Control and Prevention (CDC)

Figure. Estimated Variation Over Time in Diagnostic Tests for Detection of SARS-CoV-2 Infection Relative to Symptom Onset



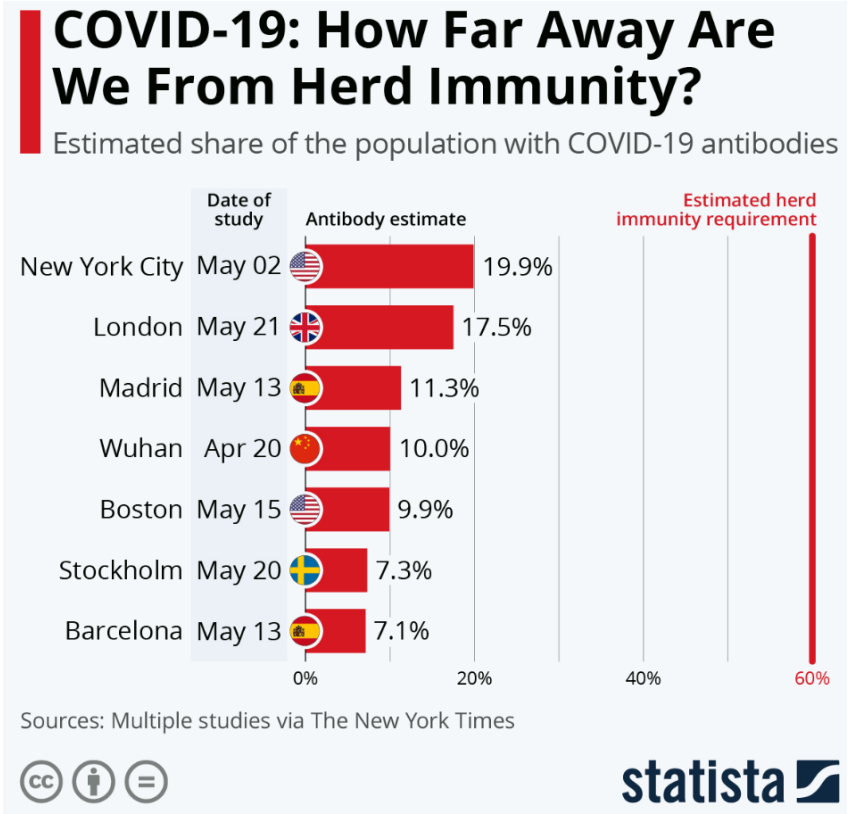
N Sethuraman, JAMA June 9, 2020

“Immunity passports” in the context of COVID-19

Scientific brief
24 April 2020

World Health Organization

At this point in the pandemic, there is not enough evidence about the effectiveness of antibody-mediated immunity to guarantee the accuracy of an “immunity passport” or “risk-free certificate.” People who assume that they are immune to a second infection because they have received a positive test result may ignore public health advice. The use of such certificates may therefore increase the risks of continued transmission. As new evidence becomes available, WHO will update this scientific brief.



https://cdn.statcdn.com/Infographic/images/normal/21866.jpeg
May 29, 2020

Why SARS-CoV-2 antibody test?

- To help define previous exposure to SARS-CoV-2 in populations
- To identify highly reactive human donors for convalescent plasma therapy
- To investigate correlates of protection

고려대학교의료원
KOREA UNIVERSITY MEDICINE

Thank you for your attention!

Professor Yunjung Cho

eqcho1ku@korea.ac.kr