The Daily COVID-19 Literature Surveillance Summary

January 19, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

Transmission & Prevention

- Genomic evidence of points to in-flight transmission of SARS-CoV-2 despite predeparture testing. A study by the New Zealand Ministry of Health looking at the points of infection and transmission of SARS-CoV-2 in 86 people returning to New Zealand through an international flight from Dubai, UAE. Passengers were placed in managed isolation and quarantine and tested for SARS-CoV-2 on their third and twelfth day after their return; 7 passengers subsequently tested positive for COVID-19. Through contract tracing, Viral genome sequencing, examining seating plans, and dates of disease onset, in-flight transmission was indicated, demonstrating the potential risk of transmission during long-haul flights despite a negative pre-departure test and reported in-flight use of mask and gloves.

TABLE OF CONTENTS

CLIMATE

GLOBAL

THE BENEFITS AND COSTS OF SOCIAL DISTANCING IN HIGH- AND LOW-INCOME COUNTRIES

Barnett-Howell Z, Watson OJ, Mobarak AM.. Trans R Soc Trop Med Hyg. 2021 Jan 13:traa140. doi: 10.1093/trstmh/traa140. Online ahead of print.
Level of Evidence: 5 - Modeling

BLUF

Social scientists from The Yale Research Initiative on Innovation and Scale and an epidemiologist from Imperial College London created an epidemiologic model to assess costs and benefits of five pandemic mitigation policies (see summary) in 178 countries. They found social distancing policies decreased mortality more profoundly in high-income countries with older populations (Figures 1, 2) and provided less value to low-income countries at the expense of the economy (Table 1). Authors suggest policy makers consider social and economic factors when implementing pandemic mitigation strategies, as residents of countries with limited resources may suffer more from loss of income than COVID-19.

SUMMARY

The 5 different non-pharmacological intervention scenarios:
- Uncontrolled spread of SARS-CoV-2 with high infectivity.
- Individual distancing policies with a 15% reduction on infectivity eg. Sweden.
- Broad social distancing policy with 35% reduction in infectivity.
- Social distancing+ with staying at home laws with 50% reduction in infectivity.
- Full-lockdown policies with 60% reduction in infectivity.

ABSTRACT

BACKGROUND: Widespread social distancing and lockdowns of everyday activity have been the primary policy prescription across many countries throughout the coronavirus disease 2019 (COVID-19) pandemic. Despite their uniformity, these measures may be differentially valuable for different countries. METHODS: We use a compartmental epidemiological model to project the spread of COVID-19 across policy scenarios in high- and low-income countries. We embed estimates of the welfare value of disease avoidance into the epidemiological projections to estimate the return to more stringent lockdown policies. RESULTS: Social distancing measures that 'flatten the curve' of the disease provide immense welfare value in upper-income countries. However, social distancing policies deliver significantly less value in lower-income countries that have younger populations, which are less vulnerable to COVID-19. Equally important, social distancing mandates a trade-off between disease risk and economic activity. Poorer people are less able to make those economic sacrifices. CONCLUSIONS: The epidemiological and welfare value of social distancing is smaller in lower-income countries and such policies may exact a heavy toll on the poorest and most vulnerable. Workers in the informal sector often lack the resources and social protections that enable them to isolate themselves until the virus passes. By limiting these households' ability to earn a living, social distancing can lead to an increase in hunger, deprivation, and related mortality and morbidity.

FIGURES

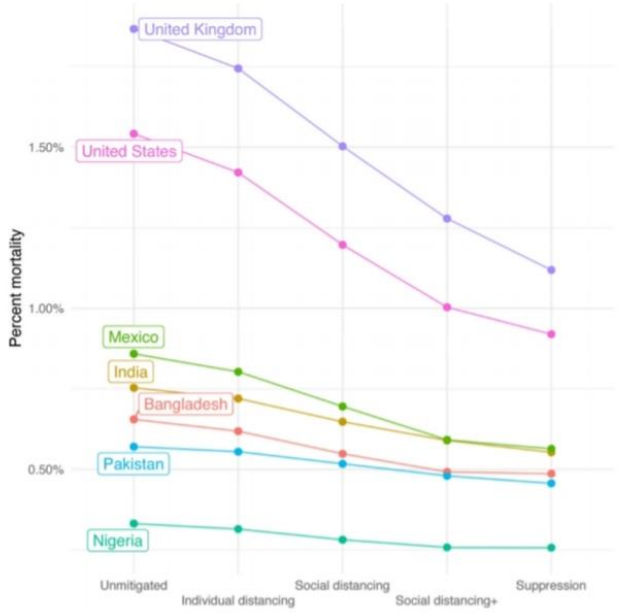


Figure 1: "The total mortality risk from COVID-19 by country. Note: Point estimates of total COVID-19 population mortality in each country are derived from the squire model under increasing levels of policy intervention".

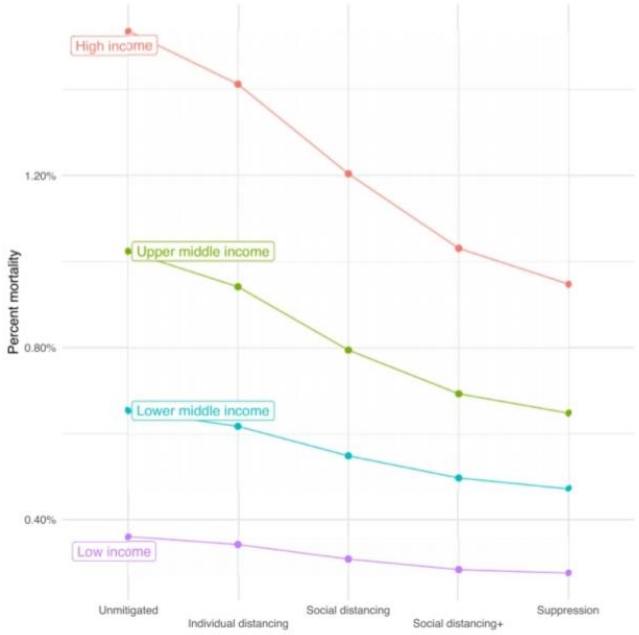


Figure 2: "Mortality risk by income group and intervention. Note: Point estimates of total COVID-19 population mortality are derived from the squire model under increasing levels of policy intervention, aggregated by World Bank income classification".

	Income group								
	High		Upper-middle		Lower-middle				Low
Strategy	UK	USA	Mexico	South Africa	India	Bangladesh	Pakistan	Nigeria	Nepal
Unmitigated	–	–	–	–	–	–	–	–	–
Individual distancing	21.7	18.6	9.8	7.5	4.6	4.5	2.7	4.2	3.7
Social distancing	42.9	34.8	19.0	13.0	10.0	8.6	6.6	8.4	7.9
Social distancing+	39.8	30.1	18.3	7.9	8.1	7.0	6.5	6.0	7.0
Suppression	28.3	13.0	4.9	2.1	5.2	0.7	4.1	0.2	1.5

Table 1: "Marginal value of COVID-19 interventions (ΔVSL/GDP)".

SARS-COV-2 INFECTION IN THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM-ASSOCIATED MORBIDITIES AND THEIR POTENTIAL MECHANISM

Karuppan MKM, Devadoss D, Nair M, Chand HS, Lakshmana MK.. Mol Neurobiol. 2021 Jan 13. doi: 10.1007/s12035-020-02245-1. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

Immunologists and molecular biologists from the Alzheimer's Disease Research Unit in the Department of Immunology and Nano-Medicine at Florida International University review neurological problems associated with SARS-CoV-2 infection (Table 1), including anosmia, encephalitis, and stroke. They propose that a downregulation in ACE2-mediated signaling along with an increase in ACE1-mediated neuroinflammation may explain the virus's neurotrophic properties (Figure 2). The authors suggest that more research is needed in order to more precisely identify a mechanism for these observed sequelae and initiate proper therapy.

ABSTRACT

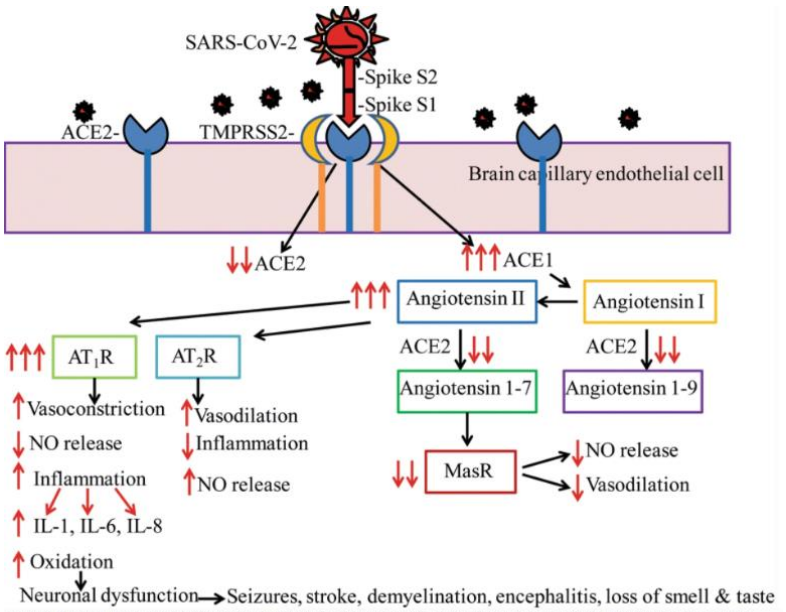
The recent outbreak of SARS-CoV-2 infections that causes coronavirus-induced disease of 2019 (COVID-19) is the defining and unprecedented global health crisis of our time in both the scale and magnitude. Although the respiratory tract is the primary target of SARS-CoV-2, accumulating evidence suggests that the virus may also invade both the central nervous system (CNS) and the peripheral nervous system (PNS) leading to numerous neurological issues including some serious complications such as seizures, encephalitis, and loss of consciousness. Here, we present a comprehensive review of the currently known role of SARS-CoV-2 and identify all the neurological problems reported among the COVID-19 case reports throughout the world. The virus might gain entry into the CNS either through the trans-synaptic route via the olfactory neurons or through the damaged endothelium in the brain microvasculature using the ACE2 receptor potentiated by neuropilin-1 (NRP-1). The most critical of all symptoms appear to be the spontaneous loss of breathing in some COVID-19 patients. This might be indicative of a dysfunction within the cardiopulmonary regulatory centers in the brainstem. These pioneering studies, thus, lay a strong foundation for more in-depth basic and clinical research required to confirm the role of SARS-CoV-2 infection in neurodegeneration of critical brain regulatory centers.

FIGURES

Table 1 Nervous system-associated morbidities in COVID-19 patients

From: SARS-CoV-2 Infection in the Central and Peripheral Nervous System-Associated Morbidities and Their Potential Mechanism

No	Morbidity	Affected region	Reference
1	Encephalitis	CSF	63, 64
2	Brain edema	Brainstem	65
3	Ischemic stroke	Cortex	71
4	Brain hemorrhage	Temporal lobe	73
5	Demyelinating lesion	Spinal cord	76
6	Impaired consciousness	Whole brain	71
7	Anosmia	Olfactory neurons	93
8	Seizures	Left temporoparietal lobe	99–101
9	Guillain-Barré Syndrome	Peripheral nerve demyelination	102–109
10	Anosmia	Olfactory epithelium	115–118
11	Ageusia	Tongue nerves	115–118
12	Headache	Whole brain	66, 69, 71
13	Myalgia-muscle pain	Neuromuscular junction	110, 111
14	delirium	Whole brain	112
15	Rhabdomyolysis	Muscle	113
16	Dizziness	Whole brain	114
17	Confusion	Whole brain	11

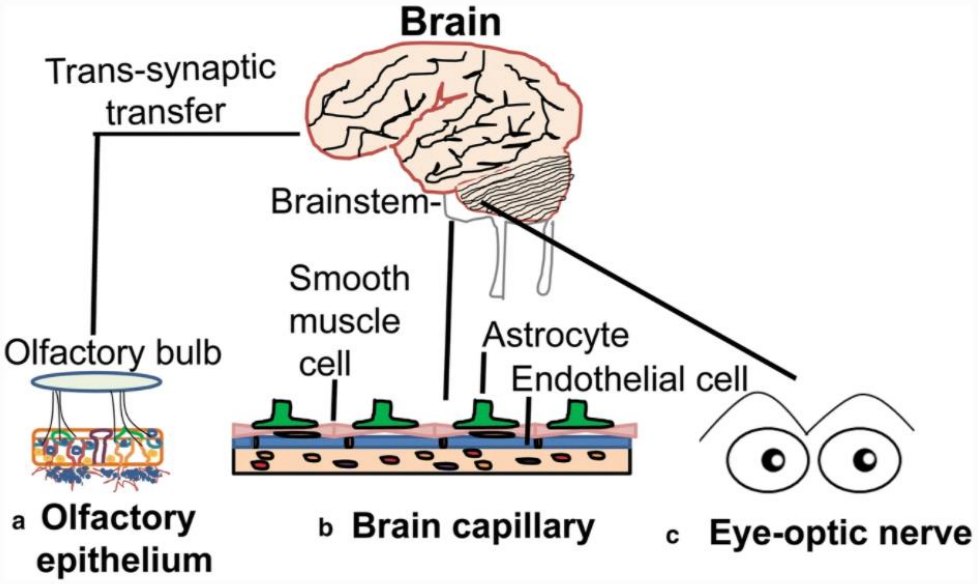


SARS-CoV-2-mediated neurodegeneration may be due to the downregulation of ACE2-mediated signaling and concomitant increase in ACE1-mediated neuroinflammation. SARS-CoV-2 binds ACE2 through the receptor-binding domain (RBD) of spike protein S_1 facilitated by protease TMPRSS2, resulting in reduced functional ACE2 expression which in turn enhances ACE1 signaling including increased conversion of angiotensin I to angiotensin II. ACE2 is responsible for the conversion of angiotensin I into angiotensin 1-9 which increases nitric oxide (NO) generation and vasodilation. With reduced ACE2, angiotensin 1-9 levels are reduced and therefore NO generation is also reduced. ACE2 is also responsible for the conversion of angiotensin II into angiotensin 1-7 which enhances Mas receptor (MasR) signaling to increase vasodilation and to prevent fibrosis. With the reduction in ACE2, MasR signaling is also reduced. Increased angiotensin II levels due to decreased ACE2 activity can also enhance signaling through the type-1a (AT_1R) or type-2 (AT_2R) angiotensin receptors. Activation of AT_2R is normally neuroprotective. However, increased AT_1R signaling leads to reduced NO generation, and therefore vasoconstriction, AT_1R signaling also increases oxidative stress and neuroinflammation with the overproduction of interleukins such as IL-1, IL-6, IL-8, and IL-29, all of which were confirmed in COVID-19 patients. Increased neuroinflammation in turn can cause neurodegeneration, brain dysfunction, and a variety of neurological issues as seen among COVID-19 patients. A schematic representation of a signal transduction mechanism is shown for endothelial cells of brain capillaries, and a similar mechanism is also expected in neurons and glia which also has been shown to express ACE2

Figure 2: see caption below image

Fig. 1

From: SARS-CoV-2 Infection in the Central and Peripheral Nervous System-Associated Morbidities and Their Potential Mechanism



Potential routes of SARS-CoV-2 entry into the brain. (A) Loss of smell sensation in many of the COVID-19 patients as one of the initial sy65mptoms suggests that the most likely route of viral entry to the brain may be through the olfactory epithelial cells, which abundantly express ACE2, followed by transmission to the olfactory bulb and higher brain regions through trans-synaptic transfer. This mechanism bypasses the BBB. (B) Viral entry through the brain capillary endothelial cells is also likely as they too express very high levels of ACE2. Once endothelial cells are damaged by viral overproduction, the virus can sneak through the underlying smooth muscle cells and finally to astrocytes, microglia, and neurons which also express ACE2. (C) The identification of viral particles in the ocular fluid in some COVID-19 patients also indicates SARS-CoV-2 can infect eyes and through the optic nerve may reach the occipital cortex and other areas of the brain including the brainstem

UNDERSTANDING THE PATHOLOGY

AN OVERVIEW OF VIRUSES DISCOVERED OVER THE LAST DECADES AND DRUG DEVELOPMENT FOR THE CURRENT PANDEMIC

Mirza AZ, Shamshad H, Osra FA, Habeebullah TM, Morad M.. Eur J Pharmacol. 2021 Jan 5;890:173746. doi: 10.1016/j.ejphar.2020.173746. Epub 2020 Nov 19.
Level of Evidence: 5 - Review / Literature Review

BLUF

Researchers from Umm Al-Qura University (Saudi Arabia) and University of Karachi (Pakistan) provide an extensive review of the etiology, pathogenesis, and treatments for several viruses including: paramyxoviruses, menangle, reovirus, pegiviruses, lyssavirus, herpesvirus, adenoviridae, astrovirus, hantavirus, human parainfluenza virus, arbovirus, anello virus, and coronaviruses. With an emphasis on coronaviruses, the authors summarize the current knowledge and latest treatments being used to combat COVID-19 and call for future research and increased societal awareness of transmission and prevention measures, highlighting high-risk animals that historically have caused epidemics. They also suggest continued technology-driven computation of detailed viral structure in drug and vaccine development against many coronaviruses including MERS, SARS, and SARS-CoV-2.

ABSTRACT

Since the discovery of the yellow fever virus in 1901, thus far, two hundred nineteen viral species are recognized as human pathogens. Each year, the number of viruses causing infections in humans increases, triggering epidemics and pandemics, such as the current COVID-19 pandemic. Pointing to bats as the natural host, in 2019, a genome highly identical to a bat coronavirus (COVID-19) spread all over the world, and the World Health Organization (WHO) officially confirmed it as a pandemic. The virus mainly spreads through the respiratory tract, uses angiotensin-converting enzyme 2 (ACE2) as a receptor, and is characterized by symptoms of fever, cough, and fatigue. Antivirals and vaccines have provided improvements in some cases, but the discovery of a new and diverse variety of viruses with outbreaks has posed a challenge in timely treatments for medical scientists. Currently, few specific antiviral strategies are being used, and many of the effective antiviral drugs and reported active molecules are under vital exploration. In this review, with the details of viral diseases, we summarize the current attempts in drug development, epidemiology, and the latest treatments and scientific advancements to combat the COVID-19 epidemic. Moreover, we discuss ways to reduce epidemics and pandemics in the near future.

SARS-COV-2 RNA IN WASTEWATER SETTLED SOLIDS IS ASSOCIATED WITH COVID-19 CASES IN A LARGE URBAN SEWERSHED

Graham KE, Loeb SK, Wolfe MK, Catoe D, Sinnott-Armstrong N, Kim S, Yamahara KM, Sassoubre LM, Mendoza Grijalva LM, Roldan-Hernandez L, Langenfeld K, Wigginton KR, Boehm AB.. Environ Sci Technol. 2021 Jan 5;55(1):488-498. doi: 10.1021/acs.est.0c06191. Epub 2020 Dec 7.
Level of Evidence: 3 - Local non-random sample

BLUF

A cross-sectional study conducted by researchers from Stanford University, University of San Francisco, and University of Michigan at the Palo Alto Regional Water Quality Control Plant and San Jose-Santa Clara Regional Wastewater Facility from March to July 2020 analyzed samples of influent and settled solids collected from each wastewater facility. They failed to detect the N1 and N2 targets for SARS-CoV-2 in the influent samples with quantitative reverse transcription PCR (RT-QPCR) but did find such targets in settled solid samples (See Figure 1), most consistently with differential-display reverse transcription PCR (ddRT-PCR) results (See Figure 2), indicating more sensitive detection of SARS-CoV-2 with settled solid samples. These findings suggest the use of settled solids in water-based epidemiology to be able to inform public health responses and prevalence of infection given the presence of SARS-CoV-2 RNA in fecal matter in sewersheds.

ABSTRACT

Wastewater-based epidemiology may be useful for informing public health response to viral diseases like COVID-19 caused by SARS-CoV-2. We quantified SARS-CoV-2 RNA in wastewater influent and primary settled solids in two wastewater treatment plants to inform the preanalytical and analytical approaches and to assess whether influent or solids harbored more viral targets. The primary settled solids samples resulted in higher SARS-CoV-2 detection frequencies than the corresponding influent samples. Likewise, SARS-CoV-2 RNA was more readily detected in solids using one-step digital droplet (dd)RT-PCR than with two-step RT-QPCR and two-step ddRT-PCR, likely owing to reduced inhibition with the one-step ddRT-PCR assay. We subsequently analyzed a longitudinal time series of 89 settled solids samples from a single plant for SARS-CoV-2 RNA as well as coronavirus recovery (bovine coronavirus) and fecal strength (pepper mild mottle virus) controls. SARS-CoV-2 RNA targets N1 and N2 concentrations correlated positively and significantly with COVID-19 clinically confirmed case counts in the sewershed. Together, the results demonstrate that measuring SARS-CoV-2 RNA concentrations in settled solids may be a more sensitive approach than measuring SARS-CoV-2 in influent.

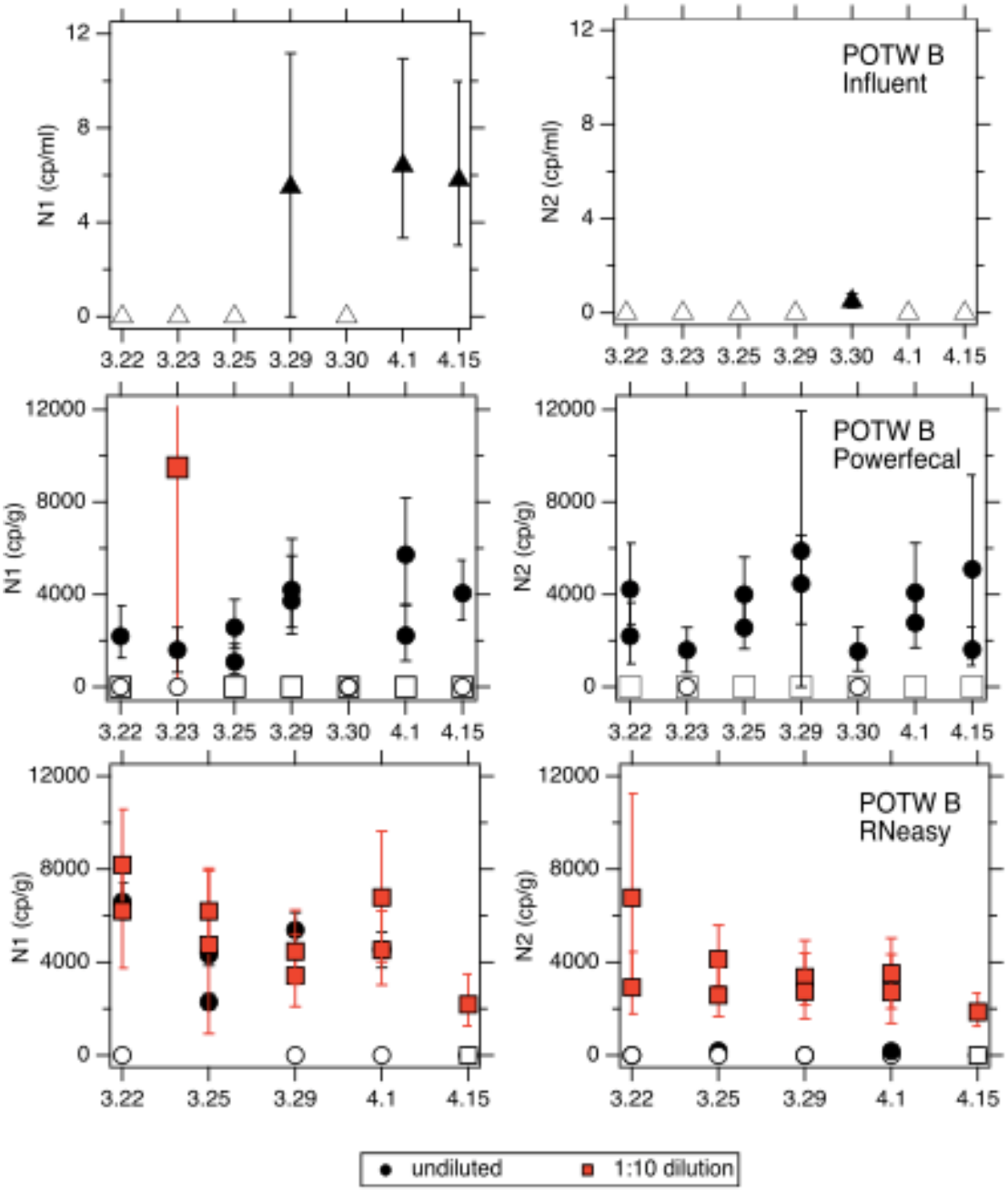


Figure 1. N1 and N2 measured at POTW B using ddRT-PCR. Top row: concentrations in influent in units of copies (cp) per mL. Middle row: concentrations in solids extracted using the powerfecal kit in units of cp per g of dry weight. Bottom row: concentrations in solids extracted using the RNeasy kit in units of cp per g of dry weight. Open symbols indicate those where no target was detected (less than three positive droplets). Error bars represent standard deviations as represented by the "total error", which includes the Poisson error and differences among merged wells. Results for undiluted and 1:10 diluted templates are provided for the solids; results for influent are for the 1:10 diluted template for N1 and the undiluted template for N2 results for influent dilutions not shown are all nondetects.

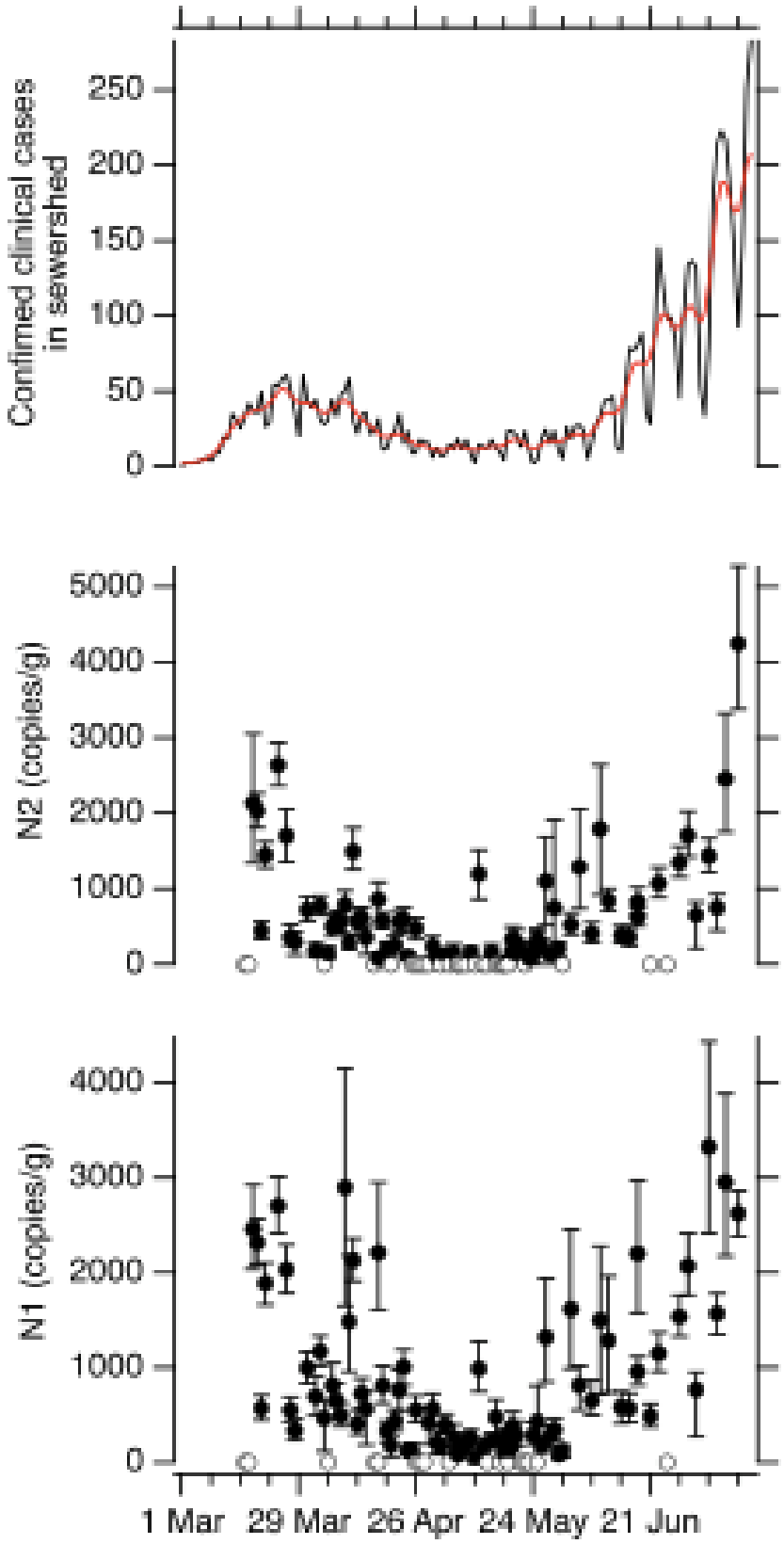


Figure 2. Top panel: confirmed new cases of COVID-19 in the sewershed of POTW B (black) and 7 day smoothed new cases (red). Middle and bottom panels: concentrations of N1 and N2 measured in solids (copies per g of dry weight). Error bars are standard deviations as total errors from the ddPCR machine. Open symbols are nondetects plotted at 0. The theoretical lowest concentration measurable is ~40 copies/g of dry weight. N1 and N2 normalized by PMMoV can be found in Figure S8.

GENOMIC EVIDENCE OF IN-FLIGHT TRANSMISSION OF SARS-COV-2 DESPITE PREDEPARTURE TESTING

Swadi T, Geoghegan JL, Devine T, McElnay C, Sherwood J, Shoemack P, Ren X, Storey M, Jefferies S, Smit E, Hadfield J, Kenny A, Jelley L, Sporle A, McNeill A, Reynolds GE, Mouldey K, Lowe L, Sonder G, Drummond AJ, Huang S, Welch D, Holmes EC, French N, Simpson CR, de Ligt J.. Emerg Infect Dis. 2021 Jan 5;27(3). doi: 10.3201/eid2703.204714. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

A study by the New Zealand Ministry of Health looking at the points of infection and transmission of SARS-CoV-2 in 86 people returning to New Zealand through an international flight from Dubai, UAE. Passengers were placed in managed isolation and quarantine and tested for SARS-CoV-2 on their third and twelfth day after their return; 7 passengers subsequently tested positive for COVID-19 (Figure 1). Through contract tracing, Viral genome sequencing, examining seating plans, and dates of disease onset, in-flight transmission was indicated, demonstrating the potential risk of transmission during long-haul flights despite a negative pre-departure test and reported in-flight use of mask and gloves.

SUMMARY

Though analyzing the onset of disease, seating plans, viral genome, the authors determined that among the 7 passengers, 2 were probably infected before the flight, 4 were probably infected in-flight, and 1 could've been infected after the flight in the managed isolation and quarantine facility.

ABSTRACT

Since the first wave of coronavirus disease in March 2020, citizens and permanent residents returning to New Zealand have been required to undergo managed isolation and quarantine (MIQ) for 14 days and mandatory testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of October 20, 2020, of 62,698 arrivals, testing of persons in MIQ had identified 215 cases of SARS-CoV-2 infection. Among 86 passengers on a flight from Dubai, United Arab Emirates, that arrived in New Zealand on September 29, test results were positive for 7 persons in MIQ. These passengers originated from 5 different countries before a layover in Dubai; 5 had negative predeparture SARS-CoV-2 test results. To assess possible points of infection, we analyzed information about their journeys, disease progression, and virus genomic data. All 7 SARS-CoV-2 genomes were genetically identical, except for a single mutation in 1 sample. Despite predeparture testing, multiple instances of in-flight SARS-CoV-2 transmission are likely.

FIGURES

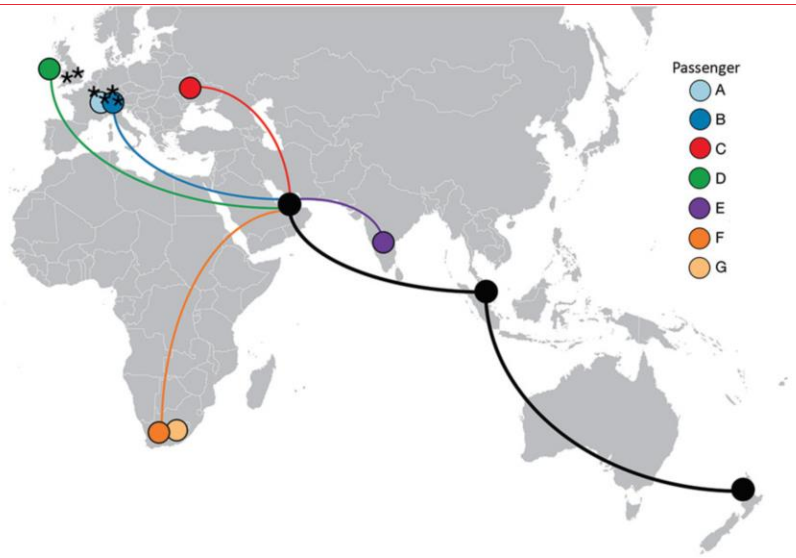


Figure 1. Countries of travel origins for 7 passengers who tested positive for severe acute respiratory syndrome coronavirus 2 infection after traveling on the same flight (EK448) from Dubai, United Arab Emirates, to Auckland, New Zealand, with a refueling stop in Kuala Lumpur, Malaysia, on September 29, 2020. Asterisks indicate where 6 other genetically identical genomes have been reported (5).

FIRST GENOME SEQUENCING OF SARS-COV-2 RECOVERED FROM AN INFECTED CAT AND ITS OWNER IN LATIN AMERICA

Carlos RSA, Mariano APM, Maciel BM, Gadelha SR, de Melo Silva M, Belitardo EMMA, Rocha DJPG, de Almeida JPP, Pacheco LGC, Aguiar ERGR, Fehlberg HF, Albuquerque GR.. Transbound Emerg Dis. 2021 Jan 9. doi: 10.1111/tbed.13984. Online ahead of print.
Level of Evidence: 5 - Case Report

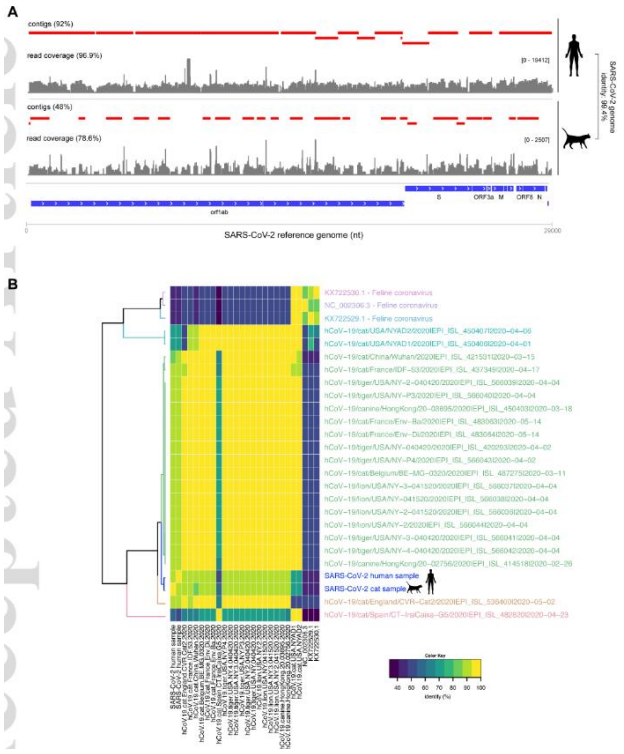
BLUF

Biologists from the University of Santa Cruz in Ilhéus-BA, Brazil present the case of a vaccinated, mixed-breed, 11 year-old male cat who had an RT-PCR SARS-CoV-2 positive rectal sample two days after his owners were confirmed to have SARS-CoV-2. They sent human and feline samples for Next Generation Sequencing and found an average sequence identity of 99.4% (Figure 1). Authors suggest that while the cat likely caught SARS-CoV-2 from his owners, cat to human transmission is still very rare and should not be a reason to abandon pets.

ABSTRACT

An 11 years-old male mixed-breed cat, with exclusively indoor life, presented 3 cough episodes after the owners tested positive by RT-PCR for SARS-CoV-2. The house is inhabited by 5 people (3 adults and 2 children), and 2 of the adults have shown mild symptoms associated with throat discomfort. The cat was vaccinated, had no history of any previous disease, and tested negative for Feline Coronavirus (FCoV), Feline Immunodeficiency Virus (FIV) and Feline Leukemia Virus (FeLV). Rectal sample collected from the cat was positive for SARS-CoV-2 by RT-PCR. Viral genome sequences recovered from human and cat samples showed an average 99.4% sequence identity. This is the first report of genome sequences of SARS-CoV-2 recovered from a cat and its owner in Latin America.

FIGURES



'Figure 1. Genomic analysis of SARS-CoV-2 genomes isolated from cat or human samples.' (A) Contig coverage of samples derived from cat or human. Contigs assembled are shown in red segments. Density of reads covering SARS-CoV-2 reference genome is shown in grey. Percentage of Coronavirus reference genome covered by assembled contigs or reads are shown within parenthesis. Scale of read density is indicated within brackets. Viral sequences from human and cat showed an average 99.4% sequence identity. (B) Hierarchical clustering based on percent identity matrix calculated from multiple alignment of Spike gene recovered from SARS-CoV-2 identified in cat or human samples, other mammals and Feline coronavirus. Sketch of human or cat in the clustering indicate the position of the viral species derived from each organism in the clade. NCBI nucleotide or GISAID database accessions are indicated on the heatmap.

CURRENT ADVANCES IN THE DETECTION OF COVID-19 AND EVALUATION OF THE HUMORAL RESPONSE

Huergo MAC, Thanh NTK.. Analyst. 2021 Jan 7. doi: 10.1039/d0an01686a. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A physical chemist and biophysicist from University College London and the National Univesity of La Plata reviewed current diagnostics used for detection of SARS-CoV-2 and associated immune responses (Figure 2). They evaluate methods for direct virus detection (RT-PCR, isothermal amplification techniques, CRISPR assays, genomic hybridization, antigen detection)(Table 1) and serology determinations (ELISA, lateral flow immuno-assay, protein microarrays)(Table 2). While they argue PCR is the gold standard test for its specificity and sensitivity, authors recommend further work to develop other sensitive diagnostic methods, particularly more accessible point-of-care tests and serology assays.

ABSTRACT

The new outbreak caused by coronavirus SARS-CoV-2 started at the end of 2019 and was declared a pandemic in March 2020. Since then, several diagnostic approaches have been re-adapted, and also improved from the previous detections of SARS and MERS coronavirus. The best strategy to handle this situation seems to rely on a triad of detection methods: (i) highly sensitive and specific techniques as the gold standard method, (ii) easier and faster point of care tests accessible for large population screening, and (iii) serology assays to complement the direct detection and to use for surveillance. In this study, we assessed the techniques and tests described in the literature, their advantages and disadvantages, and the interpretation of the results. Quantitative reverse transcription polymerase chain reaction (RT-qPCR) is undoubtedly the gold standard technique utilized not only for diagnostics, but also as a standard for comparison and validation of newer approaches. Other nucleic acid amplification methods have been shown to be adequate as point of care (POC) diagnostic tests with similar performance as RT-qPCR. The analysis of seroconversion with immunotests shows the complexity of the immune response to COVID-19. The detection of anti-SARS-CoV-2 antibodies can also help to detect previously infected asymptomatic individuals with negative RT-qPCR tests. Nevertheless, more controlled serology cohort studies should be performed as soon as possible to understand the immune response to SARS-CoV-2.

FIGURES

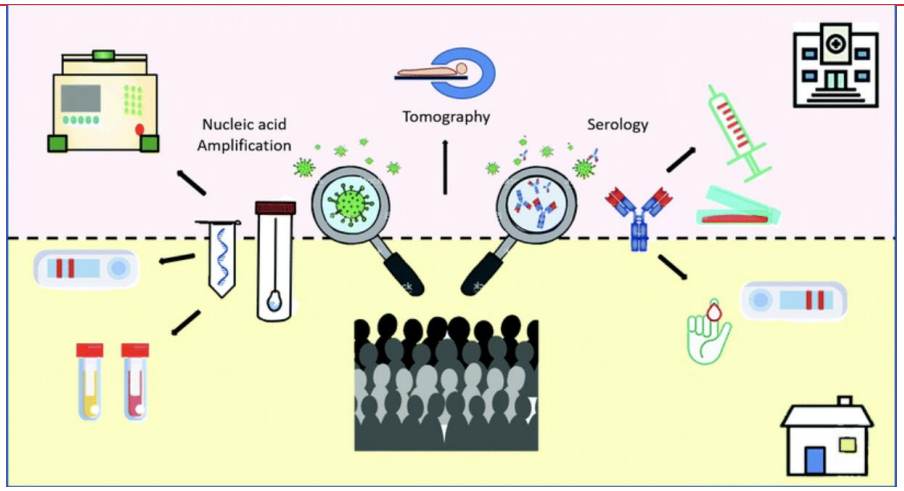


Figure 2: Schematic illustration of the diagnosis triad in pandemic situations. The upper part of the graphic (pink) represents the diagnostic methods that require central-laboratories and technology. The bottom part (yellow) represents the utilization of POC tests for direct SARS-CoV-2, the serological determinations of COVID-19, and the surveillance of large populations.

Table 1 Some of the available detection tests based on polymerase chain reaction

Test and institution	Gene/region target	Limit of detection (LoD)	Ref.
Centre for disease control and prevention, China	*ORF1ab* and *N*	1.5 copies per reaction	62
Charité virology, Berlin, Germany	*RdRp*, *E* and *N*	5.2; 3.8; 8.3 copies per reaction respectively	18 and 63
School of Public Health, LKS Faculty of Medicine, University of Hongkong, China	*ORF1b* and *N*	<10 copies per reaction	45
Beijing Wantai Biological Pharmacy Enterprise Co. Lt	*ORF1b* and *N*	1–10 copies per reaction	61
Seegene Inc. Allplex™ 2019-nCoV assay	*RdRp*, *E* and *N*	1–10 copies per reaction	61
RT-qPCR, National Institute of Infectious Disease	*N gene*	5 copies per reaction	64 and 65
CDC 2019 novel coronavirus (nCoV) real-time RT-PCR	*N1* and *N2*	~31 and 6 copies per reaction	44
Institut Pasteur	*RdRp* and *E*	10 copies per reaction	66
Boditech Med. Inc ExAmplar COVID-19 real-time PCR kit	*E* gene *RdRp gene*	10–50 copies per reaction 50–100 copies per reaction	54 and 61
COVID-19-RdRp/Hel RT-PCR assay	*RdRP*/*Helicase*	11.2 copies per reaction	43
Simplexa	*S* and *ORF1ab*	500 copies per mL	67
nCoV-QS (MiCo BioMed)	*ORF3a* and *N*	1.8 and 4.24 copies per mL	68
Shanghai Kehua Bio-Engineering Co. Ltd KHB diagnostic kit	*ORF1ab*, *N* and *E*	1–10 copies per reaction	61
BGI Health (HK) Co. Ltd, RT-PCR kit for detection 2019-nCOV (CE-IVD)	*ORF1 gene*	1–10 copiesper reaction	61
The Rutgers Clinical Genomics Laboratory SARS-CoV-2 Assay	*ORF1ab*, *S* and *N*	200 copies per mL	52
bioMérieux SA ARGENE® SARS-COV-2 R-GENE®	*RdRp* and *N*	1–50 copies per reaction	61
Tib Molbiol/Roche Diagnostic Multiplex RNA Virus Master	*E gene*	1–10 copies per reaction	61
RealStar® SARS-CoV-2 RT-PCR kit (Altona Diagnostics)	*E*: betacoronavirus *E- S*: SARS-CoV-2	1–10 copies per reaction 1–10 copies per reaction	69
RT-PCR + restriction fragment length polymorphism	*RdRp* and *E*	204 and 70 copies per reaction respectively	70
COVID-19-nsp2	Non-structural protein 2 (*nsp2*)	1.8 $TCID_{50}$ per mL	71

Table 2 Some of the available detection tests based on immunoassays

Method	Antigen	Antibody	Signalling method	Ref.
Microarray	67 antigens	Multitarget IgG	Fluorescence	134
Magnetic chemiluminescence enzyme immunoassay (MCLIA)	*S* and *N* proteins	IgM and IgG	Chemiluminescence	135 and 136
ELISA Euroimmun	*S1* domain	IgA and IgG	Absorbance	136–138
ELISA, COVID-AR	Nucleoprotein *N*	IgM and IgG	Absorbance (HRP)	139
LFIA, Avioq	Not reported	IgM and IgG	Naked-eye with AuNPs	136
ELISA	Protein S	IgM and IgG	Absorbance (HRP)	140
LFIA	*RBD*	IgM and IgG	Naked-eye with AuNPs	141
CLIA Abbot	Nucleoprotein *N*	IgG	Chemiluminescence	138 and 142
Time-resolved fluorescence Immunochromatography assay	Not reported	IgM and IgG	Fluorescence	143
ELISA	*RBD* and trimeric protein *S*	IgM and IgG	Absorbance (HRP)	144 and 145
Double Sandwich ELISA	*RDB*	Total and IgM	Absorbance (HRP)	146
Indirect ELISA	Nucleoprotein *N*	IgG		
Indirect ELISA	Nucleoprotein *N*	IgA, IgM and IgG	Absorbance	13
MCLIA	Nucleoprotein *N* and protein *S*	IgM and IgG	Chemiluminescence	23
MCLIA	*ORF1ab*, *S*, and *N*	IgM and IgG	Chemiluminescence	147
LFIA, NG-Test®	Not reported	IgM and IgG	Naked-eye with AuNPs	138
ELISA	*RBD*	Total antibody	Absorbance (HRP)	137
Indirect ELISA	*S1*, *S*, *RBD* and *N*	IgA and IgG	Absorbance (HRP)	148 and
Microarray	*S1*	Betacoronavirus	Fluorescence	149
ELISA	Trimeric protein *S*	IgM and IgG	Absorbance	150
MCLIA	*RBD* and *N*	IgA, IgM and IgG	Chemiluminescence	151
LFIA	Nucleoprotein *N*	IgG	Naked-eye with lanthanide-doped polystyrene nanoparticles	70
ELISA N	Nucleoprotein *N*	IgG	Absorbance (HRP)	152
ELISA tri-S	Trimeric protein *S*	IgA, IgM and IgG	Absorbance (HRP)	
LFIA, FarmaCoV	Nucleoprotein *N*	IgM and IgG	Naked-eye with AuNPs	153

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