INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

June 2020

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NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
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INA-RESPOND newsletter

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SENIOR WRITERS

Aly Diana

REVIEWERS & CONTRIBUTING WRITERS

Dedy Hidayat, Eka Windari R., Herman Kosasih, Kanti Laras, Lois E. Bang, Maria Intan J., M. Ikhsan Jufri, Mila Erastuti, Neneng Aini, Nurhayati, Venty M. Sari

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Badan Penelitian dan Pengembangan Kesehatan RI, Gedung 4, Lantai 5.
Jl. Percetakan Negara no.29,
Jakarta 10560

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FEATURES

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CLINICAL TRIAL REGISTRATION – BRING OUR RESULTS INTO THE LIGHT

By: Aly Diana

All journals listed to follow the International Committee of Medical Journal Editors (ICMJE) recommendation will only consider trials beginning on or after July 1, 2005, if registration occurred before the first patient was enrolled ("prospective registration"). Yes, we have been far away from 2005; so, the only way to get our hard work during a clinical trial to be published is to register our trials before we start. Most journals no longer give any exception to register a clinical trial when we want to publish. I am sure all of us know that we must register, what do we do know why (on top of being published)?

Before we are talking about the "why," let's see the definition first. A clinical trial is defined as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects of health outcomes. Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration.

The registration of all interventional trials is considered to be a scientific, ethical, and moral responsibility because of good reasons. Firstly, there is a need to ensure that decisions about health care are informed by all of the available evidence, and it is difficult to make informed decisions if publication bias and selective reporting are present. Secondly, describing clinical trials in progress can make it easier to identify gaps in clinical trial research. Enabling researchers and health care practitioners to identify trials in which they may have an interest could result in more effective collaboration among researchers. The type of collaboration may include a prospective meta-analysis. Thirdly, improving awareness of similar or identical trials will make it possible for researchers and funding agencies to avoid unnecessary duplication (it means saving a lot of money!). Next, making researchers and potential participants aware of recruiting trials may facilitate recruitment. Lastly (for now), registries checking data as part of the registration process may lead to improvements in the quality of clinical trials by making it possible to identify potential problems (such as problematic randomization methods) early in the research process.

We can see that registration is an important thing to do, but we also need to understand that this is a debatable issue, particularly for the pharmaceutical industries. Most of the pharmaceutical companies hesitate to register their clinical trial because of the (a) fear of intellectual property being plagiarized, (b) loss of market value of the investigational medical product, (c) disinclination to release sensitive information earlier to the general public, (d) compromise of the profit due to availability of information to the competitors. Although these concerns prevail in the industry, the revised Declaration of Helsinki, which is widely regarded as the cornerstone document on human research ethics, states that "every clinical trial must be registered in a publicly accessible database before recruitment of the first subject." Regardless of the concerns, compliance to international standards is mandatory; and transparency is the key for a greater good.

To check which trials registries are acceptable to the ICMJE, please check this website: http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/ and https://www.who.int/ictrp/network/primary/en/

Good luck!

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INA-RESPOND Newsletter

TRIPOD & INA-PROACTIVE Study Updates

By: Eka Windari R., Lois E. Bang, Maria Intan Josi, M. Ikhsan Jufri, Venty Muliana Sari

STUDY UPDATES

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PARTICIPANT STATUS

Per 01 Jun 2020, the total ongoing participants in the TRIPOD study are 40 out of 490 enrolled participants. From those 40 ongoing participants, 19 are still on TB treatment while 21 are waiting for their 6-month post-treatment visit. Two hundred and sixteen participants have completed the study, while 234 participants are terminated early (including death). Therefore, there are still 8.1 % of participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, all participants from site 520 have completed the study. There are 1 participant from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar) who still needs to be followed up, 20 participants from site 560 (RSUP dr. Kariadi Semarang), 1 participant from site 570 (RSUD dr. Soetomo Surabaya), 8 participants from site 580 (RSUP dr. Sardjito Jogjakarta), 9 participants from site 590 (RSUP Persahabatan Jakarta), and 1 participant from site 600 (RSUP dr. Adam Malik Medan).

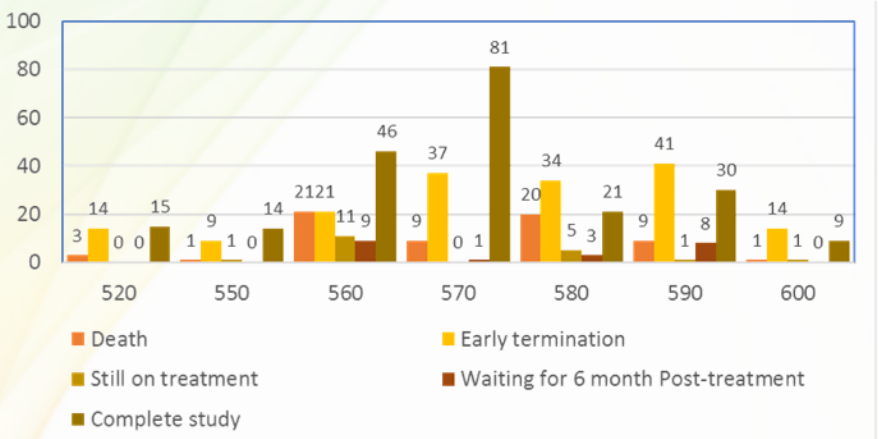

Figure 1.Participant status per site based on uploaded CRF per 1 June 2020

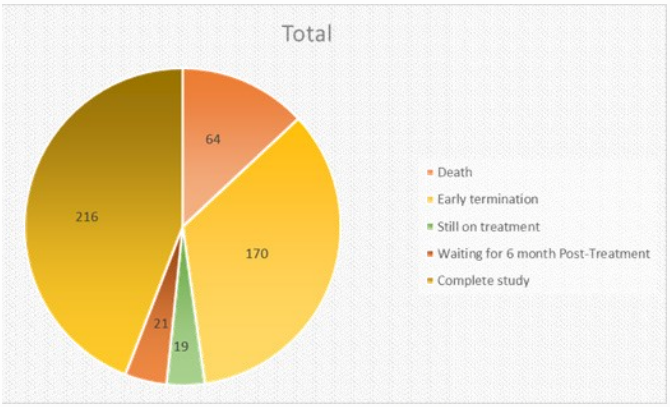

Figure 2. Total participant status based on uploaded CRF per 1 June 2020

TRIPOD MANUSCRIPT

The authors for the TRIPOD manuscript has been selected. In the near future, a meeting with NIH will be performed to initiate the progress. The following are several manuscripts that being planned: a) focus on the baseline findings; b) treatment outcome and the related affected factors; c) related factors of TB and DM co-morbidity. The authors will be sorted according to enrolled participants. A discussion will be set up during the Clinical Research Protocol Writing Workshop.

Site number	Site name	Author
520	RS Sanglah Denpasar	dr. I Gede Ketut Sajinadiyasa, Sp.PD
550	RSUP dr. Wahidin Sudirohusodo	Dr. dr. Irawaty Djaharuddin, SpP(K)
560	RSUP dr. Kariadi	dr. Banteng Hanang Wibisono, Sp.PD-KP
570	RSUD dr. Soetomo	dr. Tutik Kusmiati, SpP (K)
580	RSUP dr. Sardjito	dr Bambang Sigit Riyanto, SpPD-KP, FINASIM
590	RSUP Persahabatan	dr. Diah Handayani, SpP
600	RSUP H Adam Malik	Dr. dr. Bintang YM Sinaga, M.Ked(Paru), Sp.P(K)

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Currently, the screening, enrollment, and follow up activities of INA-PROACTIVE study are still on temporary halt until further notice. However, to avoid any missed visit for subjects who have reached maximum window period or those who might have difficulties to go to the Site because of PSBB (large scale social restriction), Sites may continue to arrange subject follow up by prioritizing safety and following the coronavirus disease prevention and control protocol.

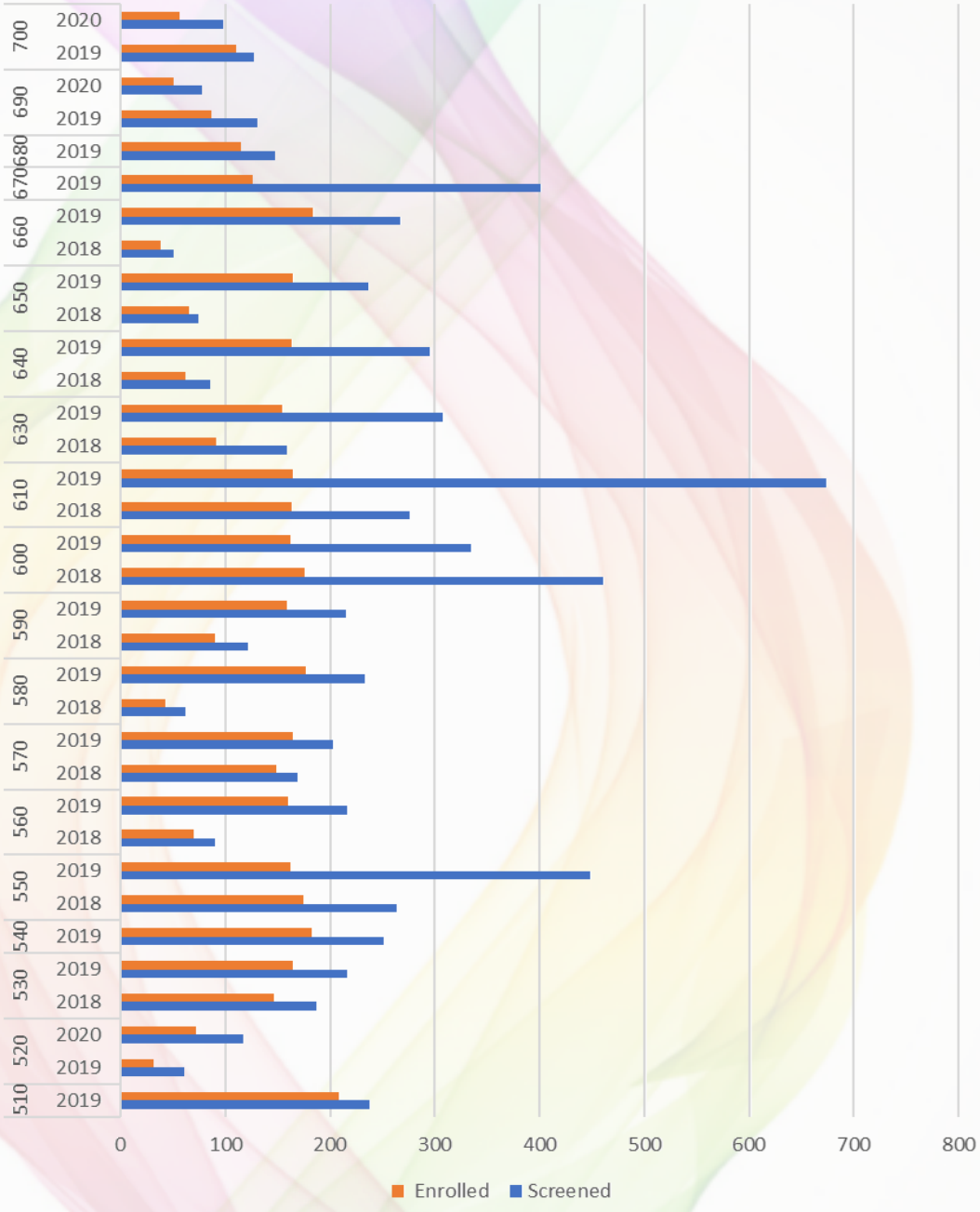


Figure 1. All Site Number Screened vs Enrolled

Furthermore, two of the three last activated sites whose enrollment period will end on 30 Jun 2020 have been approved by Secretariat to continue the subject enrollment; these are site 520 (Sanglah Hospital in Bali) and site 700 (TC Hillers Hospital in Maumere). Site 690 (Abepura Hospital in Papua) has decided not to continue the subject enrollment due to Hospital policy regarding COVID-19 Pandemic. By 7 Jun, 4,290 subjects had been enrolled, which consisted of 4,104 adults and 186 pediatrics from a total of 7,302 subjects screened. Details are shown in figure 1.

During the enrollment and follow up halt, some sites are working on completion of study data such as missing logs, syntax data, and study disposition status. For sites that have been monitored remotely, they are working on the monitoring action item resolution. The next remote monitoring is planned for Site 650 (Budi Kemuliaan Hospital, Batam) on 22-24 Jun 2020, followed by Site 600 (Adam Malik Hospital) on 25-26 Jun 2020, and Site 640 (St.Carolus Hospital) on 29-30 Jun 2020.

INA-RESPOND Newsletter

SITE PROFILE: RSUD dr. T.C Hillers Maumere

By: Andre Mahardhika H. and Sandy Grace Tindage

SITE PROFILE

Maumere is the central city of the Sikka district on the island of Flores, East Nusa Tenggara (NTT). The town is famous for its dance/song *'goyang' Maumere* (*gemu famire*) and traditional woven cloth crafts. The handwork of the craftsmen truly reflects Maumere's original culture that has not been touched by modernization. The natural purity of the sea and the hills in this city is still maintained. They have not been ruined by human hands. The traditional culture of Maumere has not undergone cultural assimilation with other regions, so its cultural uniqueness is very much felt.

The city of Maumere has been a health reference for the people of Flores island since 1953. RSUD dr. TC Hillers has served a variety of patients from the city of Maumere and other towns on the island of Flores. According to the Minister of Health's decree in 1993, RSUD dr. TC Hillers is designated as a regional referral hospital in NTT. One of the several research the hospital participated in is malaria research.

In 2019, INA-RESPOND began its collaboration at dr. TC Hillers General Hospital. The INA-RESPOND site 700 team carries out their daily activities in a room next to the VCT clinic. This six-by-three-meter room is filled with various research documents, equipment, and supplies., the laboratory and freezer, located in a different building, are only 150 meters from the VCT clinic.

Principal Investigator

Name: dr. Asep Purnama, Sp.PD, FINASIM.

Place and Date of birth: Blitar, January 1967.

Formal Education: Medical Faculty of Udayana University (S1 and specialist).

dr. Asep Purnama Sp.PD, FINASIM, is the Head of the internal medicine department at RSUD dr. TC Hillers. In addition to his positions at the hospital, he is

dr. Asep Purnama, Sp.PD, FINASIM

also an advisor for Sikka IDI. PI site 700 is a passionate and fatherly figure. His wisdom, enthusiasm, and idealism drive doctors in Sikka Regency to pursue knowledge as much as possible. His open and welcoming nature invites people to be engaged in a discussion, either work or life-related actively.

Co-PI

Name: dr. Mario B. Realino Nara, Sp.A

Place and Date of birth: Makassar, August 1969

Formal Education: Medical Faculty of Airlangga University (S1 and specialist)

dr. Mario B. Realino Nara, Sp. A is the Head of the children's department of RSUD dr. TC Hillers and the Chairman of IDI Sikka. He is calm and authoritative but friendly to many people. Although there are not many pediatric subjects in our study, he is diligent and detailed with all his patients.

Co-PI

Name : dr. Dwi Kurniawan Nugroho, M.Sc.,Sp.PK

Place and Date of birth: Semarang, May 11th 1973

Formal Education: Medical Faculty of Gadjah Mada University (S1 and specialist)

dr, Dwi Kurniawan Nugroho, M.Sc, Sp.PK is the Head of the clinical laboratory of RSUD dr. TC Hillers. This UGM -graduate doctor is a hardworking person. Discipline and perseverance are his main principles. He is also kind of a comic. Any serious talk can be lightened by him.

Research Assistant (RA) 1

Name: dr. Andre Mahardhika Harsono

Place and Date of birth: Bogor, August 1993

Formal Education: Medical Faculty of Airlangga University (S1)

dr. Andre Mahardhika Harsono is the first RA at site 700. He comes from Solo, Central Java, and it makes total sense if he is a polite and calm man. Philosophy, theology, and politics are his favored topics.

Research Assistant 2

Name: dr. Sandy Grace Tindage

Place and Date of birth: Surabaya, April 1991

Formal Education: Medical Faculty of Atmajaya University (S1)

dr. Sandy Grace Tindage is the second RA at the Maumere site. She is from the city of Surabaya, East Java. As a Research Assistant, dr. Sandy is a cheerful figure. Her joyfulness can always brighten the atmosphere. She also has a passion for cooking and traveling. Her love for the Eastern Indonesian region brought this reliable doctor to the land of Sikka, Maumere city.

Continue to page 9

From top to bottom, left to right: dr. Mario B. Realino Nara, Sp.A, dr. Dwi Kurniawan Nugroho, M.Sc.,Sp.PK, dr. Andre Mahardhika Harsono, dr. Sandy Grace Tindage, study team members during EC Monitoring.

INA-RESPOND Newsletter

PROACTIVE LOG PAGES

By: Michael Duvenhage

FROM OUR SPONSOR

The PROACTIVE study has various log pages that are extremely important and should please be completed in a timely manner and as accurately as possible. It is important to understand how the log pages relates to other CRF pages and how specific data items might require additional information to be completed on the log pages. The PROACTIVE study has the following log pages:

- Log 200 - Past & Current Illnesses
- Log 300 - Laboratory Hematology Results
- Log 400 - Laboratory Diagnostic Results
- Log 500 - Sputum Examination / Chest X-Ray
- Log 600 - Other Supporting Evaluation Results (If Available)
- Log 700 - HIV-ARV Medications
- Log 800 - ARV Side Effects
- Log 900 - Other Therapy (Non-ARV), Including Side Effects
- Log 1000 - Drugs Allergies

Please note that we will not discuss all the log pages in this newsletter, however we are focusing on the current issues that the INA-RESPOND DM team has noticed with the various log pages.

Log 200 – Past & Current Illnesses

It is important to update Log 200 with the corresponding records if any of the following questions were answered as indicated on the following CRFs:

- If there is a TB history in Baseline & Enrollment → CRF Page 8.0

Apakah subyek pernah didiagnosis TB sebelum ikut penelitian ini? / *Has the participant ever been diagnosed with TB before enrollment?* ☐1 Ya* / *Yes** ☐0 Tidak / *No* ☐66 Tidak tahu / *Unknown*

- If subject's clinical staging at HIV diagnosis is III or IV → CRF Page 6.0

Stadium Klinis HIV saat didiagnosis HIV pertama kali / *HIV clinical staging at first HIV diagnosis:*
☐1 I ☐2 II ☐3 III ☐4 IV ☐66 Tidak ada data / *No Data*

- If subject's current clinical staging is III or IV → CRF Page 9.0

Stadium Klinis HIV / *HIV clinical stage:* ☐1 I ☐2 II ☐3 III ☐4 IV ☐66 Tidak tahu / *Unknown*

Please remember to complete any other past and current illnesses as well per participant source documents and study requirements.

Log 500 - Sputum Examination / Chest X-Ray

Please complete the various sputum examinations and chest x-rays on Log 500. It is also important to consider the question on CRF page 8.0:

Tipe TB, **tandai semua yang sesuai** / *Type of TB, **mark all that apply**:*
☐1 TB paru / *Pulmonary TB* → Isi log "Sputum & Chest X-Ray" / *Fill log "Sputum & Chest X-Ray"*
☐2 TB ekstra paru, jelaskan **(tandai semua yang sesuai)** / *Extra pulmonary TB, specify **(mark all that apply)**:*

If the participants had/have pulmonary TB history at Baseline/ Enrollment then there should be an corresponding sputum examination records and/or Chest X-Ray records on the log page.

Log 700 - HIV-ARV Medications

All participants enrolled into the PROACTIVE study should have this log page completed.

Please add corresponding data for every HIV-ARV medication the participant is taking. Please remember to update start/end dates and any HIV-ARV medication regimen changes.

Log 800 - ARV Side Effects

When completing the ARV Side Effects it is extremely important to consider the data as completed on log 700 – HIV-ARV Medication.

PENGGUNAAN ARV / *HIV-ARV MEDICATIONS*

Kode ARV / *ARV Code* (Rujuk ke CRFCG/ *Refer to CRF CG*)	Alasan penggunaan ARV *Reasons of ARV use**		Kode FDC/ *FDC code*	Tanggal mulai *Start Date* / (TGL/ BLN/ THN *DD/MMM/YYYY*)	Tanggal berhenti / *End Date* (TGL/ BLN/ THN) / *(DD/MMM/YYYY)*	Berlanjut / *Ongoing*	Kode Follow up/ *follow up code*	Kode alasan ARV dihentikan/ diganti *Reasons of stopping/ changing ARV code*
	Kode / *Code*	Jika lainnya, jelaskan / *If Other, specify*						
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
_ _ _ _ _ _	__	_____	__	_-_-_____	_-_-_____	☐1	__	__
_ _ _ _ _ _	__	_____	__	_-_-_____	_-_-_____	☐1	__	__
_ _ _ _ _ _	__	_____	__	_-_-_____	_-_-_____	☐1	__	__

Example of log 700.

Please note that there should be a corresponding ARV side effect record for each HIV-ARV medication that is listed on log 700. Additionally the ARV side effect record dates match the timeframe (start/end dates) as listed n log 700. Additionally any changes in HIV-ARV medications as listed on log 700 should have corresponding records on the ARV side effects log 800 page.

Lastly, please note that the ARV Side Effects log page also track

HIV-ARV compliance thus each record (as already explained) should carefully match the timeframe as documented on log 700.

Log 900 - Other Therapy (Non-ARV), Including Side Effects

There is a direct relationship between Log 200 (Past & Current Illnesses) and Log 900 – Other Therapy (non-ARV medication).

Please complete any other therapies (non-ARV medication) on this log page as it relates back to log 200.

Questions:

Please contact the PROACTIVE study data manager for any questions related to the log pages at serari@ina-respond.net

PENYAKIT DAHULU & SEKARANG / *PAST & CURRENT ILLNESSES*

Kode Penyakit / *Disease code* (Rujuk ke CRFCG/ *Refer to CRF CG*)	ICD-10	Status	Diagnosis	IRIS check	TB IRIS	Pemeriksaan pendukung (utk diagnosis definitive/presumtif) / *Supporting evidence for definitive/presumtive diagnosis*	Tanggal diagn. (TGL/BLN/THN) / *Diagnosed Date (DD/MMM/YYYY)*	Tanggal berhenti (TGL/BLN/THN) / *Stop Date (DD/MMM/YYYY)*	Berlanjut / *Ongoing*	Dirawat RS/ *Hospitalized*	Operasi / *Surgery*
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
_ _ _ _ _ _	_____	__	__	__	__	_____	__/__/____	__/__/____	☐1	☐1	☐1
_ _ _ _ _ _	_____	__	__	__	__	_____	__/__/____	__/__/____	☐1	☐1	☐1
_ _ _ _ _ _	_____	__	__	__	__	_____	__/__/____	__/__/____	☐1	☐1	☐1

Example of log 200

Continued from p.7 (Site Profile)

Lab Technicians (LT)

Name: Fransisca Matilde, AMAk

Place and Date of birth: Maumere, April 1969

Formal Education: Faculty of Health, Muhammadiyah University (D3)

Fransisca Mathilde, AMAk is the chief of clinical laboratory staff at the RSUD dr. TC Hillers. She is better known as '*Mama Ida*.' Mama Ida is the "leader" of our LTs at INA-RESPOND. She becomes a mother figure to the Research Assistants as she loves listening to their stories.

Name: Stefani Marwah Sari Tolok, AMAk

Place and Date of birth: Maumere, October 1987

Formal Education: Mohammad Husni Thamrin School of Health (D3)

Stefani Marwah Sari Tolok, AMAk is a young staff of clinical laboratory at RSUD dr. TC Hillers. We usually call her by 'Kak Fany.' Although her figure is tiny, she has a big heart. She is easy to get along and loves to make jokes. Everybody loves her.

Name : Kurniawati Handayani Koli, S.ST

Place and Date of birth : Maumere, March 1987

Formal Education : Bhakti Wiyata Kediri Institute of Health (D4)

Kurniawati Handayani Koli, S.ST, a.k.a '*Kak Nia*' is a young clinical laboratory staff of RSUD dr. TC Hillers. We sometimes tease her by referring to her as a "walking convenience store." Kak Nia offers many items to sell to her friends. We can find Tupperware, clothes, silverware, and many other things from her. RAs also love buying things from her.

Research Nurse

Name: Maria Yupina Yuanti, AMK

Place and Date of birth: Wukur, February 1972

Formal Education: Academy of Nursing, Health Polytechnic Kupang (D3)

Maria Yupina Yuanti, AMK is the only nurse in the VCT clinic of RSUD dr. TC Hillers. '*Mama Yanti*' is easy to get along with people and often becomes the conversation partner of RAs. Her memory is excellent. She can memorize all patients treated at VCT. She quickly becomes an essential source of information for RAs related to the condition and whereabouts of our study subjects.

Name : Febronius Raymundus, S.Kep

Birth Place and Birth Date: Maumere, February 1982 Formal Education: Health Polytechnic Kupang (S1)

Febronius Raymundus, S.Kep is one of the 'all-rounder' nurses at RSUD dr. TC Hillers. He takes care of and handles many things, ranging from patient's administration, TB clinics, VCT clinics, and management. He is also the Secretary of IDI Sikka and holds a lot of information about the administration of doctors and patients in Sikka.

INA-RESPOND Newsletter

DIAGNOSTIC ASPECT OF COVID-19 (PART 2)

By: Yan Mardian

SCIENCE CORNER

I. SEROLOGY TEST

COVID-19 infection can also be detected indirectly by measuring the host immune response to SARS- CoV-2 infection. Serological diagnosis is especially important for patients with mild to moderate illness who may present late, beyond the first 2 weeks of illness onset. Serological diagnosis also is becoming an important tool to understand the extent of COVID-19 in the community and to identify individuals who are immune and potentially "protected" from becoming infected, including those that may be asymptomatic or have recovered. Serology tests are blood-based tests that can be used to identify whether people have been exposed to a particular pathogen by looking at their immune response. In contrast, the RT-PCR tests currently being used globally to diagnose cases of COVID -19 can only indicate the presence of viral material during infection and will not indicate if a person was infected and subsequently recovered. These tests can give greater detail into the prevalence of a disease in a population by identifying individuals who have developed antibodies to the virus.

When serology testing is used for diagnostic, surveillance, or epidemiological purposes, antibodies and antigens are the 2 serum proteins of interest. Antibodies are specialized Y-shaped proteins, also known as immunoglobulins, that recognize foreign particles (antigens) located on microbial surfaces. Antibodies either mark microbes for destruction by immune cells or the complement system or target and eliminate them directly. This process is specific. A given antibody recognizes and binds to its corresponding antigen in a manner analogous to a lock and key mechanism. Seroconversion is the development of detectable antibodies in the blood against a particular antigen. It takes 1-2 weeks post symptom onset for patients to seroconvert to SARS-CoV-2.

COVID-19 serology testing relies on targeted antibodies binding to SARS-CoV-2-specific antigens. Blood serum is collected and applied to a testing platform that contains copies of viral antigen. Capillary action draws the blood through the device where it mixes with the antigens. If the patient has developed antibodies in their blood against SARS-CoV-2, the corresponding antibodies will recognize and bind to the antigens, indicating past exposure to SARS-CoV-2. Accurate interpretation of serology testing depend on antigen specificity, but also on the type of antibody being detected. Humans have 5 different classes of antibodies, and each plays a unique role in immunity. IgM, IgG, IgA and total antibody count are the primary targets of COVID-19 serology tests. The biological properties of these isotypes are distinguished below. Research to define the temporal kinetics of antibodies against SARS-CoV-2 is ongoing.

IgM is one of the first antibodies produced during infection. It can be expressed in monomeric form on the surface of B lymphocytes or found circulating in the blood and lymphatic fluid in pentameric form. The IgM pentamer consists of 5 antibodies joined together to form a ring-like-structure. This structure, coupled with the fact that the antigen-binding site of IgM is not highly specific, allows for simultaneous binding of multiple antigens and rapid clearing from the bloodstream during primary infection. Although IgM is the largest antibody by size, its relative abundance in the blood is only about 10% of total antibody count.

IgG is the smallest and most abundant circulating antibody. It exists in monomeric form, makes up approximately 80% of total antibody count and is primarily found in serum. IgG typically appears later in infection when mature B cells receive signals to switch from production of IgM to IgG. During the secondary immune response, IgG can have many potential roles, including direct neutralization of microbes and targeting of microbes for immune cell-mediated processes. As the most specific and long-lasting isotype, IgG is a key player in establishing post-infection immunity.

IgA is primarily responsible for protecting mucosal surfaces, exists in dimeric form and can be found in serum, mucosal secretions, saliva, tears, sweat and breast milk. Seroconversion timing for IgM and IgG varied across studies and antibody class. Production of virus-specific antibodies were detected at an early stage after symptom onset in some cases (around d 5), in other cases at the intermediate (many studies suggest seroconversion around d12-14 for IgG) or late-stage (see below) and in some patients not at all.

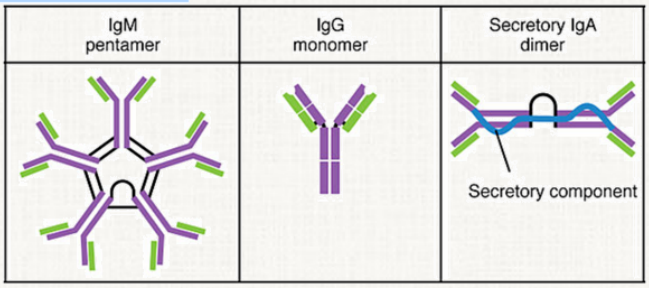
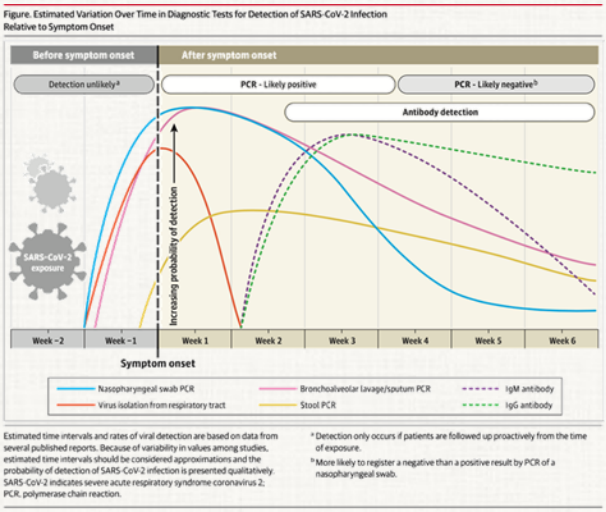


Illustration of IgM, IgG, and IgA antibody isotypes. Image adapted from OpenStax College.

Source: http://cnx.org/content/col11496/1.6/

The most sensitive and earliest serological marker is total antibodies, levels of which begin to increase from the second week of symptom onset. Although IgM and IgG ELISA have been found to be positive even as early as the fourth day after symptom onset, higher levels occur in the second and third week of illness. After infection IgM antibodies appear first and thereafter IgG. IgM levels are higher at early stages of disease and then decreases over time, while IgG levels increases during the intermediate and later stage after symptom onset. In regard to this the results from this rapid review were mixed, with some studies reporting earlier seroconversion for IgM, others for IgG, or similar seroconversion time for both antibodies. This discrepancy, may be due to different sensitivity of the tests to different antibodies, but possibly also to real variation in immune responses between patients.



For example, IgM and IgG seroconversion occurred in all patients between the third and fourth week of clinical illness onset as measured in 23 patients by To et al and 85 patients by Xiang et al. Thereafter IgM begins to decline and reaches lower levels by week 5 and almost disappears by week 7. whereas IgG persists beyond 7 weeks. In a study of 140 patients, combined sensitivity of PCR and IgM ELISA directed at nucleocapsid (NC) antigen was 98.6% vs 51.9% with a single PCR test. During the first 5.5 days, quantitative PCR had a higher positivity rate than IgM, whereas IgM ELISA had a higher positivity rate after day 5.5 of illness.

The platforms for COVID-19 serology tests on the market today include lateral flow assays (RDT), ELISA (enzyme-linked immunosorbent assays), and chemiluminescent immunoassays. These assay types differ in how they detect antibody-antigen binding. The gold standard to determine the presence of neutralizing antibodies specific to SARS-CoV-2 is by Plaque Reduction Neutralization Test (PRNT), which must be done in BSL-3, which therefore is not suitable to be conducted outside research setting.

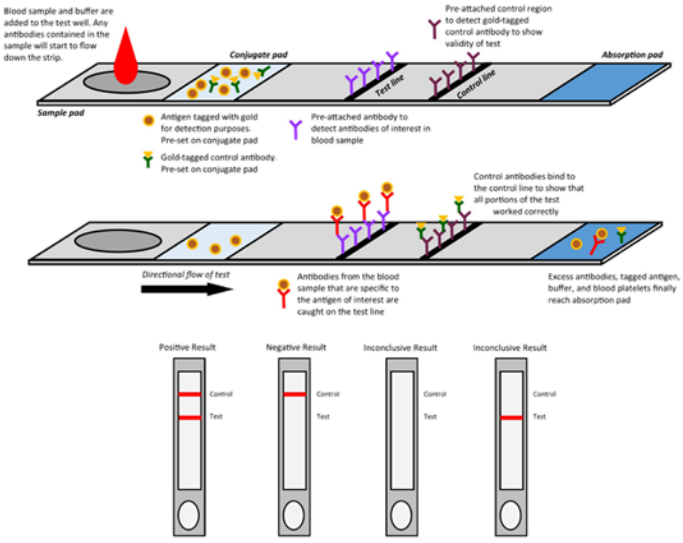
Rapid diagnostic test (RDT)

Rapid point-of-care tests for the detection of antibodies have been widely developed and marketed and area of variable quality. Detection only occurs if patients are followed up proactively from the time of exposure. More likely to register a negative than a positive result by PCR of a nasopharyngeal swab. Many manufacturers do not reveal the nature of the antigens used. These tests are purely qualitative in nature and can only indicate the presence or absence of SARS-CoV-2 antibodies.

Table 1 Characteristics of included studies that reported on seroconversion rate and timing after SARS-CoV-2 infection (N=12)

Author Year	No of patients with COVID-19: age; gender	Severity of disease§	Test for detection of SARS-CoV-2 specific antibodies	No of serum samples and time of sampling	IgM	IgG	Publication type/ Journal/Impact factor (IF)
Gao 2020 Retrospective China	N=22 Median age: 40 years (4-73) F:8; M:14	Not reported (most patients received oxygen therapy and anti-viral medication)	CLIA, ELISA, GICA * *Considered positive if one of the tests was positive[3]	N=37* d 1-7: n=10 d 8-14:n=13 d14 -24: n=14 (Some missing samples)	Seroconversion rate and timing: 1-7 d: 60% (6/10); 8-14 d: 53.8% (7/13); 14-24 d::78.6% (11/14)	Seroconversion rate and timing: 1-7 d: 50% (5/10); 8-14d: 76.9% (10/13); 14-24:d:100% (14/14)	Accepted for publication / Chinese Medical Journal/ IF: 1.053 in 2014
Jiang 2020 Cohort study China	N=29 (and 29 controls) Mean age: 42.3 (SD 13.8) F:16; M:13	3 mild cases; and 26 'common' cases	Proteome microarrays	N=29 Collected mean 22 days after onset	Seroconversion rate: 100%	Seroconversion rate: 100%	MedRxiv pre-print
Yong 2020 Retrospective China	N=34 Median age: 40.5 (IQR:31-49.5) M:53%	35 mild cases, 3 severe/critical cases	GICA	N= 76 Samples collected during hospitalisation.	Seroconversion rate: 50% (19/38)	Seroconversion rate: 92% (35/38)	MedRciv pre-print
Liu 2020 Retrospective China	N=133 Median age:68 F:63; M:70	44 moderate cases; 52 severe and 37 critical cases	SARS-CoV-2antibody detection kit	Not reported	Seroconversion rate by severity of disease: Moderate:79.55% Severe: 82.69% Critical:72.97%	Seroconversion rate by severity of disease: Moderate: 93.18% Severe:100% Critical: 97.30%	MedRxiv pre-print
Lou 2020 Cohort study China	N=80 cases and N=300 controls Median age: 55 (45-64)	65 non-critical cases and15 critical cases	ELISA, LFIA, and CMIA assays	N=304 Mean: 4 samples per/patient	Seroconversion rate & timing: 0-7d::33.3% 8-14d::86.7% 15-24d:96.7%	Seroconversion rate & timing: 0-7d: 33.3% 8-14d: 76.0% 15-24d: 93.3%	MedRxiv pre-print

This is typically a qualitative (positive or negative) lateral flow assay that is small, portable, and can be used at point of care (POC). These tests may use blood samples from a finger prick, saliva samples, or nasal swab fluids. RDTs are often similar to pregnancy tests, in that the test shows the user colored lines to indicate positive or negative results. In the context of COVID-19, these tests most frequently test for patient antibodies (IgG and IgM), or viral antigen. In some cases, it can be beneficial to measure baseline (before infection) of IgG and IgM titers.



The SARS-CoV-2 rapid IgG-IgM combined antibody test kit is a lateral flow qualitative immunoassay for the rapid determination of the presence or absence of both anti- SARS-CoV-2-IgM and anti-SARS-CoV-2-IgG in human specimens (whole blood, serum, and plasma). The test kit comes with a test cartridge, sample dilution buffer, and a package insert. The presence of SARS-CoV-2 IgG and IgM antibodies are indicated by a red/purple line in the specific region indicated on the device.

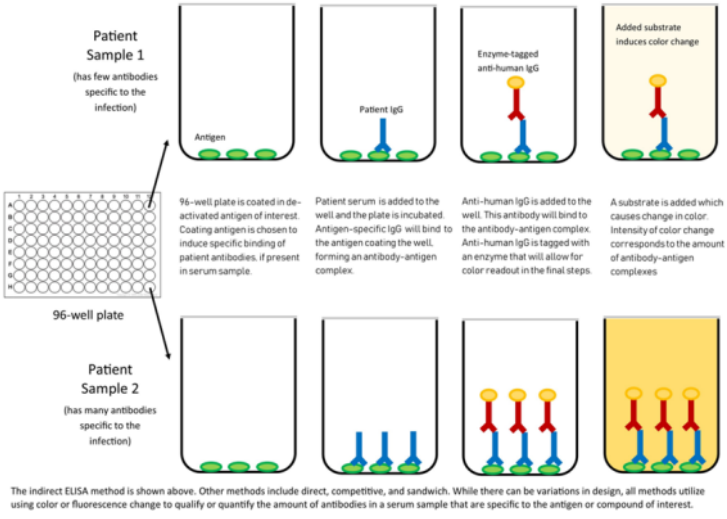
The main body of the test strip consists of five parts, including plastic backing, sample pad, conjugate pad, absorbent pad, and NC membrane. Every component of the strip should be given a pretreatment described as follows: the NC membrane was attached to a plastic backing layer for cutting and handling. A surface antigen from SARS-CoV-2 which can specifically bind to SARS-CoV-2 antibodies (including both IgM and IgG) is conjugated to colloidal gold nanoparticles and sprayed on conjugation pads. The Gold-rabbit IgG conjugates was also sprayed on conjugation pads. If IgM or IgG in the tested sample are presence, they will bind to surface antigen of SARS-CoV-2 on conjugate pads and will go through NC membrane until binding with the anti-human-IgM and anti-human-IgG in M and G line respectively, while Gold-rabbit-IgG will bind to anti-rabbit IgG antibody which is immobilized on control line (C line), as an internal control of test.

At least 27 commercially available RDT Antibody kits are undergoing dependent evaluation by FIND, Foundation for Innovative New Diagnostics, a partnership between Hôpitaux Universitaires de Genève and WHO to accelerate development and access to diagnostics as part of the global response to the COVID-19 pandemic. The results of validation test will be published on website as soon as they are available.

Enzyme-linked immunosorbent assay (ELISA):

ELISA-based IgM and IgG antibody tests have greater than 95% specificity for diagnosis of COVID-19. Testing of paired serum samples with the initial PCR and the second 2 weeks later can further increase diagnostic accuracy. Typically, the majority of antibodies are produced against the most abundant protein of the virus, which is the NC. Therefore, tests that detect antibodies to NC would be the most sensitive. However, the receptor-binding domain of S (RBD-S) protein is the host attachment protein, and antibodies to RBD-S would be more specific and are expected to be neutralizing. Therefore, using one or both antigens for detecting IgG and IgM would result in high sensitivity.

This test can be qualitative or quantitative and is generally a lab-based test. These tests usually use whole blood, plasma, or serum samples from patients. The test relies on a plate that is coated with a viral protein of interest, such as Spike protein. Patient samples are then incubated with the protein, and if the patient has antibodies to the viral protein they bind together. The bound antibody-protein complex can then be detected with another wash of antibodies that produce a color or fluorescent-based readout. In the context of COVID-19, these tests most frequently test for patient antibodies (IgG and IgM).



The list of ELISA kit undergone evaluation by FIND is listed in table 3.

Chemiluminescent immunoassay (CLIA)

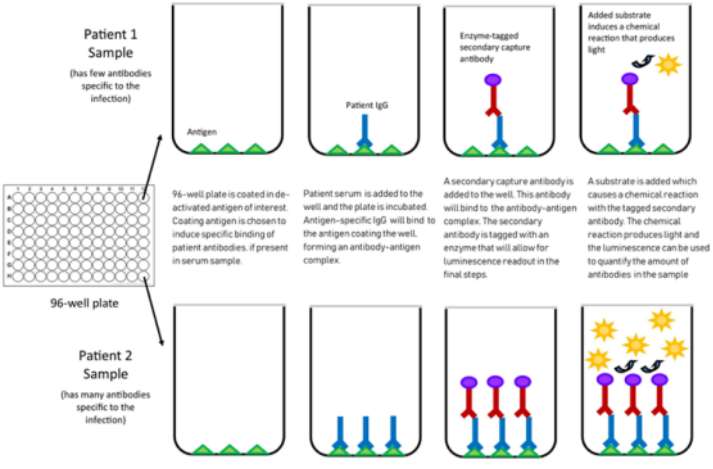
This test is typically quantitative, lab-based, and uses whole blood, plasma, or serum samples from patients. A variation of this test can use magnetic, protein-coated microparticles, known as a chemiluminescent microparticle immunoassay. The test relies on mixing

3. ELISA/Automated Immunoassays (IAs) undergoing evaluation

Company	Test	Company location	Target analyte	Regulatory status
Beijing Wantai Biological Pharmacy Enterprise Co., Ltd	Wantai SARS-CoV-2 IgM ELISA	China	IgM	CE-IVD
Beijing Wantai Biological Pharmacy Enterprise Co., Ltd	Wantai SARS-CoV-2 Ab ELISA	China	Total Ab	CE-IVD
Epitope Diagnostics, Inc.	EDI™ Novel Coronavirus COVID-19 IgG ELISA kit	USA	IgG	CE-IVD
Epitope Diagnostics, Inc.	EDI™ Novel Coronavirus COVID-19 IgM ELISA kit	USA	IgM	CE-IVD
EUROIMMUN AG	Anti-SARS-CoV-2 ELISA (IgA)	Germany	IgA	CE-IVD; Australia; Brazil
EUROIMMUN AG	Anti-SARS-CoV-2 ELISA (IgG)	Germany	IgG	CE-IVD; Australia; Brazil; USA
Guangzhou Darui Biotechnology Co., Ltd	2019 Novel Coronavirus IgG Test (ELISA)	China	IgG	CE-IVDUO
Guangzhou Darui Biotechnology Co., Ltd	2019 Novel Coronavirus IgM Test (ELISA)	China	IgM	RUO

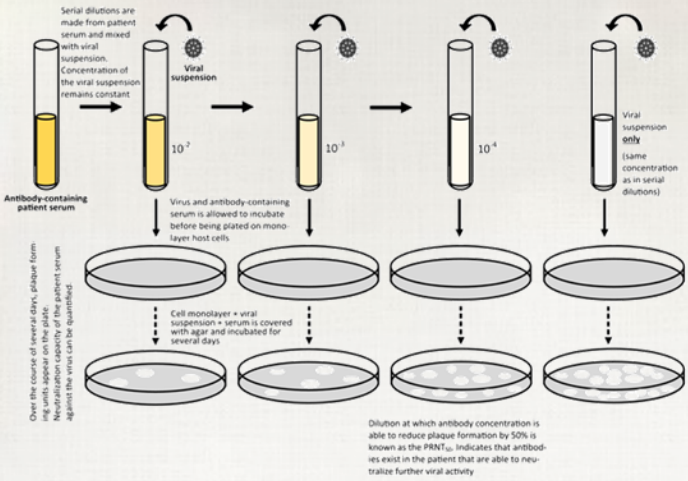
CE-IVD – conformité européenne (EU certification)-*in vitro* diagnostics
RUO – Research Use Only

patient samples with a known viral protein, buffer reagents, and specific enzyme-labeled antibodies that allow a light-based, luminescent read-out. Any antibodies in the patient sample that react to the viral protein will form a complex. Then, (secondary) enzyme-labeled antibodies are added that bind to these complexes. This binding induces a chemical reaction that produces light. The amount of light (radiance) emitted from each sample is then be used to calculate the number of antibodies present in a patient sample. This test can look for multiple types of antibodies, including IgG, IgM, and IgA.



Neutralization assay

Neutralizing antibodies are classically detected using Plaque Reduction Neutralization Tests (PRNTs). However, PRNTs require the use of live virus and must be performed in biosafety level 3 (BSL3) facilities for SARS-CoV-2. Furthermore, this type of test is challenging and time-consuming to perform. As an alternative, BSL2 neutralization tests have been developed using Pseudotyped Vesicular Stomatitis Virus (VSV) expressing SARS-CoV-2 spike (S) protein. At this time, it appears that these tests are only available for use in academic institutions and research laboratories. Neutralization assays can tell researchers if a patient has antibodies that are active and effective against the virus, even if they have already cleared the infection. These tests require whole blood, serum, or plasma samples from the patient. Neutralization assays depend on cell culture, a lab-based method of culturing cells that allow SARS-CoV-2 growth (like VeroE6 cells). When virus and cells are grown with decreasing concentrations of patient antibodies, researchers can visualize and quantify how many antibodies in the patient serum are able to block virus replication. This blocking action can happen through the antibody binding to an important cell entry protein on the virus, for example.



Cross-Reactivity Concerns

COVID-19 serology assays are designed to be specific for SARS-CoV-2, but how do we know they will not cross-react with other coronaviruses? Cross-reactivity with the common coronaviruses (cCoV's) would be especially detrimental since 60-75% of children have antibodies to one or more hCoV's, and 90% of adults over 50 years of age have antibodies to all 4 hCoV's. Fortunately, there is not a lot of sequence identity shared between SARS-CoV-2 and hCoV's (approximately 21-34% AA homology), but the FDA does require laboratories to include a note on all positive serology reports stating, "False-positive results due to antibodies to cCoV's may occur." What about the closer relatives of SARS-CoV-2? SARS-CoV-2 and SARS-CoV share 90% amino acid identity for their respective N proteins and 77% for S proteins. SARS-CoV-2 and MERS-CoV share 49% amino acid identity for N proteins and 33% for S proteins. These data highlight the value of using S protein antigens to increase the specificity of serology tests.

Predictive Values and Disease Prevalence

Positive and negative predictive values are dependent on test performance characteristics (specificity and sensitivity), as well as disease prevalence. In regions with low COVID-19 disease prevalence, the risk of false-positive results by serologic testing is higher, even with excellent specificity. Therefore, the rate of infection needs to be taken into account, and repeat testing may be useful to confirm results in populations with low disease prevalence.

Interpretation of Serology Test

Condition	Probable Interpretation	Action should be taken
IgM and IgG negative	Not yet exposed to COVID Recent infection, but not yet develop Ab False negative due to immune defect False negative due to unreliable test	Continue healthy lifestyle during pandemic Repeat the test 10-14 days later NAT (if COVID is highly suspected) Change serology assay device/test
IgM and IgG positive	Acute infection with seroconversion Resolved infection False positive due to cross-reaction False positive due to unreliable test	Confirm with NAT Confirm with NAT Check possible pathogens (e.g. Other hCOV) Change serology assay device/test
IgM only positive	Most likely recent/ acute infection	Confirm with NAT, repeat for 2nd test
IgG only positive	Most likely resolved infection	Confirm with NAT (if --ve, consider back to work?)

It's therefore valuable to conclude with a summary of the current recommended uses for serology testing:

When COVID-19 Serology Testing Should Be Used

- The primary application of serology testing is the identification of individuals who have previously been infected with SARS-CoV-2. This knowledge can be used to guide epidemiology and seroprevalence studies, as well as facilitate contact tracing.
- Serology tests may also be used to identify potential convalescent plasma donors and to evaluate the immune response to candidate vaccines.
- Finally, there is potential for serology tests to aid in the diagnosis of COVID-19 in RT-PCR negative patients who present later during disease course.

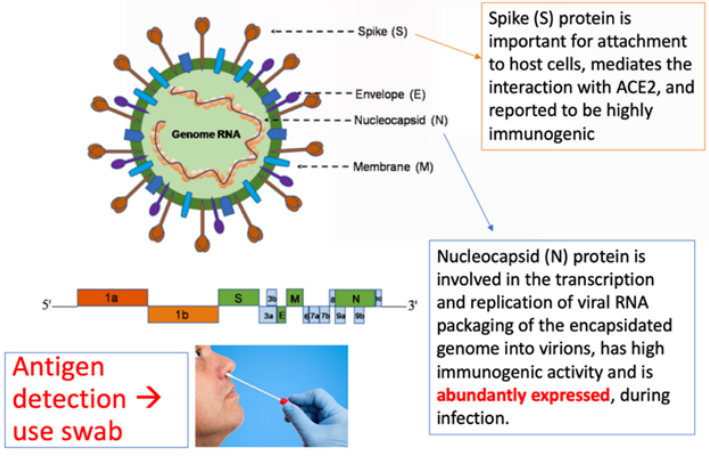
When COVID-19 Serology Testing Should NOT Be Used

- Serology testing should not be used to diagnose acute or recent cases of COVID-19.
- At this time, serology tests cannot be used to definitively determine if a patient has developed protective immunity.
- Because of the above limitations, SARS-CoV-2 serology testing should not be used to guide personal protective equipment (PPE) use or adherence to social distancing practices.

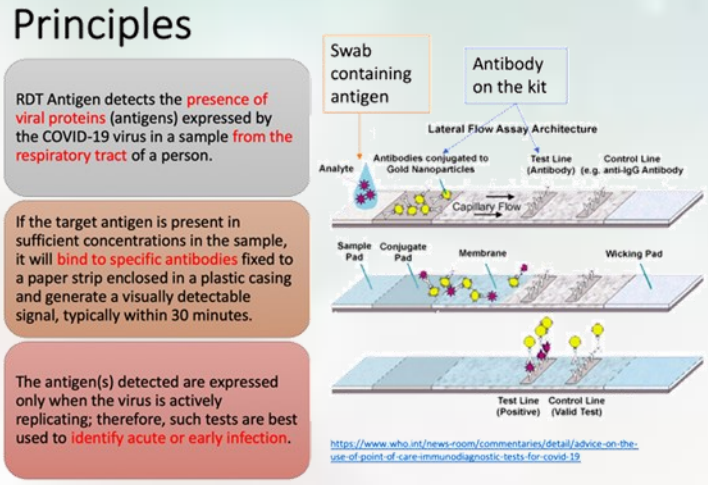
II. ANTIGEN TEST

The following viral antigens have been used for antigen testing.

- Spike Protein – Spike proteins (S proteins) are unique, mushroom-shaped surface proteins that bind host cells and mediate virus entry. Each monomer of S protein contains two subunits, S1 and S2, which facilitate attachment and membrane fusion, respectively. S1 and S2 subunits may be used individually or combined as antigens for serology testing.
- Nucleocapsid – The nucleocapsid protein (N protein) is a basic RNA-binding protein that plays structural and nonstructural roles in infection. In complex with genomic RNA, N protein forms the viral capsid of SARS-CoV-2, and data suggest it plays a number of additional roles in pathogenesis.
- Receptor Binding Domain (RBD) – RBD represents the portion of the S1 protein that binds angiotensin-converting enzyme 2 (ACE2), the human receptor for SARS-CoV-2.



RDT Antigen detects the presence of viral proteins (antigens) expressed by the COVID-19 virus in a sample from the respiratory tract of a person. If the target antigen is present in sufficient concentrations in the sample, it will bind to specific antibodies fixed to a paper strip enclosed in a plastic casing and generate a visually detectable signal, typically within 30 minutes. The antigen(s) detected are expressed only when the virus is actively replicating; therefore, such tests are best used to identify acute or early infection.



Currently available antigen test for COVID-19 are mainly divided into two types, Lateral Flow Immunoassay (LFIA) and dipstick method, as depicted below.

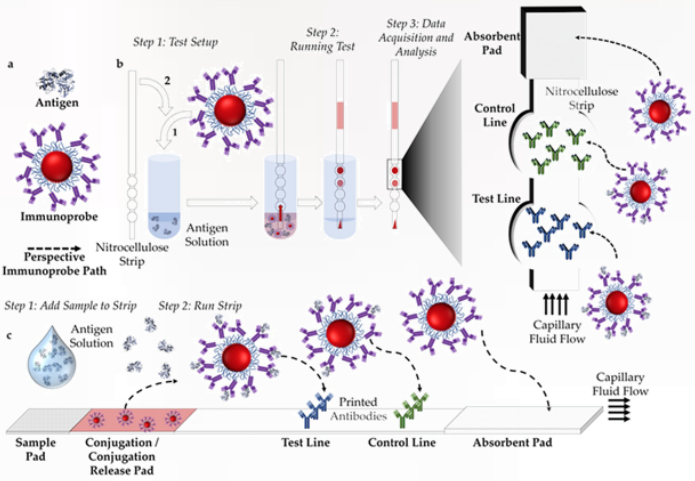


Figure 2. (a) Figure legend. (b) Schematic representation of a test run and result readout of a dipstick assay configuration. (c) Schematic representation of a test run and result readout of a lateral flow assay (LFA) configuration.

Based on the development experience of Antigen detection by ELISA for previous SARS and MERS outbreak, the protein used for detection is Nucleocapsid Protein (NP), which is preferred over Spike (S) protein because NP are secreted more abundantly at the time of virus replication, and it is also specific which made the possibility of cross-reaction with other hCoV, such as OC43 and 229E, is relatively small. Regarding the current COVID-19 pandemic, there were at least two preliminary studies published in preprinted (non-peer-reviewed) journals, for the validation of RDT Antigen kit compared with gold standard (PCR) in detecting SARS-CoV-2 on swab samples. The results of both studies show excellent specificity (98.3% - 100%), with varying overall sensitivity (48.3% -

Comparison of nucleic acid and N antigen detection among participants with nucleic acid detection CT value ≤40

COVID-19 Nucleocapsid Protein Detection \ Nucleic Acid Detection	Positive	Negative	Total
Positive	141	0	141
Negative	67	31	98
Total	208	31	239

Sensitivity: 68% Specificity: 100% Accuracy: 72% Positive Predictive Value: 100%

Negative Predictive Value: 32% Prevalence: 87% Negative Likelihood Ratio: 32%

Comparison of nucleic acid and N antigen detection among participants with nucleic acid detection CT value ≤30

COVID-19 Nucleocapsid Protein Detection \ Nucleic Acid Detection	Positive	Negative	Total
Positive	55	0	55
Negative	1	31	32
Total	56	31	87

Sensitivity: 98% Specificity: 100% Accuracy: 99% Positive Predictive Value: 100%

Negative Predictive Value: 97% Prevalence: 64% Negative Likelihood Ratio: 2%

68%), and the sensitivity is increasing in patients with high viral load (CT Value <30 (98%) on LFIA-RDT and CT value <25 (58.3% -85.7%) on Dipstick-RDT.

In line with the previous experience from the development of RDT Antigen for the detection of influenza viruses during the H1N1 pandemic, the specificity of RDT was indeed very good, but the sensitivity was relatively low (46.7% - 53.3%). It could be explained that the positivity of RDT was usually required high levels of antigen, so if the virus load was not high enough, false negative RDT Antigen results was most likely occurred. In addition, the use of polyclonal / monoclonal antibodies implanted in the RDT Antigen kit, as well as the possibility of antigen destruction on frozen / repository swab samples is also thought to contribute to the less accuracy in capturing antigens on the kit.

However, the need for the use of the SARS-CoV-2 RDT Antigen as a tool to increase testing capacity which is able to detect COVID-19 in the early stages is increasingly becoming a promising method. Therefore, the validation test on commercially available kit are urgently needed. The list of Antigen-based RDT kit undergone evaluation by FIND is listed below.

1. Antigen (Ag)-based RDTs undergoing evaluation

Company	Assay	Country of manufacturer	Interpretation	Regulatory status
Coris BioConcept	COVID-19 Ag Respi-Strip	Belgium	Visual	CE-IVD
RapiGEN, Inc.	BIOCREDIT COVID-19 Ag	Rep. of Korea	Visual	CE-IVD
SD BIOSENSOR, INC.	STANDARD F COVID-19 Ag FIA	Rep. of Korea	Reader	CE-IVD; Brazil
SD BIOSENSOR, INC.	STANDARD Q COVID-19 Ag Test	Rep. of Korea	Visual	CE-IVD; Brazil
Shenzhen Bioeasy Biotechnology Co., Ltd*	Bioeasy 2019-nCoV Ag Fluorescence Rapid Test Kit (Time-Resolved Fluorescence)	China	Reader	CE-IVD

**This fluorescence-based test is different from the colloidal gold Ag test that has now been withdrawn by the company.*

Interpretation of the Antigen test:

Condition	Probable Interpretation	Action should be taken
Antigen negative	No acute or early infection of COVID-19 False negative due to the level of extracted antigen below specificity of the test False negative due to unreliable test	Continue healthy life-style during pandemic Repeat the Ag test if symptoms worsen, or wait 10-14 days later to check Antibody Change device/kit
Antigen positive	Acute infection with active replication False positive due to cross-reaction with other pathogen False positive due to unreliable test	Confirm with NAT Confirm with NAT Change device/kit

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INA-RESPOND Newsletter

STAY ACTIVE AT HOME DURING PANDEMIC

By: Marco Ariono

In 2020, there is a worldwide outbreak of a new type of coronavirus (COVID-19), which originated from China. A study revealed that its mean incubation period was 5.2-12.5 days, and experts suggest a 14-day quarantine. The most common symptoms of this disease are fever, cough, nausea, vomiting, and diarrhea.[1,2]

Rapid and accurate detection of COVID-19 is crucial to control the outbreak. Isolation, quarantine, social distancing, and community containment can be used to curb this pandemic. Many countries shut down their public transportation, like buses, trains, ferries, and planes, in their efforts to control the spread of the virus. To 'flatten the curve,' governments have enforced border shutdowns, travel restrictions, and quarantine, which sparked fears of an impending economic crisis and recession. COVID-19 has affected societies, corporations, industries, financial markets, and the global economy.[3]

COVID-19 also has a significant impact on sporting agendas such as Euro 2020, Tokyo Olympic 2020, Premier League 2019-2020, and Liga 1 2020. The Euro 2020 and Tokyo Olympic 2020 tournaments have been postponed to 2021. Meanwhile, Premier League 2019-2020 has been scheduled to continue in June, and Liga 1 2020 is making preparations for September 2020 with various regulations. Other sports events such as golf, tennis, athletics, basketball, rugby, cycling, boxing, and badminton also face cancellations and delays in an attempt to control the spread of disease.[3]

Physical Activity during COVID-19 Pandemic

Governments have ordered citizens to stay at home to prevent further spread of the infection. Under these situations, physical and mental health problems are significant concerns. Staying home, while it is a safety measure, may lead to decreased physical activity. A study by Xiang et al. showed a substantial decrease in physical activity and an increase in screen time during the COVID -19 pandemic in children and adolescents.4,5 The prolonged stay-at-home may lead to increased sedentary behaviors, such as spending unnecessary amounts of time sitting, reclining, or lying down for screening activities like playing games, watching television, and using mobile devices, which will lead to an increased risk of chronic health conditions. It is well known that low physical activity and prolonged sedentary behavior are linked to both adverse physical and mental health outcomes such as reduced muscular and cardiorespiratory fitness, weight gain, and psychosocial problems.

We should continue being active although we are staying at home during the COVID-19 pandemic. Since outdoor exercise can become potential virus transmission, especially when there are lots of people gathering close, training at home can be a wise decision to stay active. We can use various safe, simple, and easily implementable exercises that are well suited to avoid the airborne coronavirus and maintain fitness levels. The training should include cardiorespiratory exercise, strengthening exercises, and stretching exercises. Some exercises/activities that can be done in-home are walking in the house, lifting and carrying groceries, leg lunges, stair climbing, sit-to-stand using a chair, chair squats, and sit-ups, and pushups. We also can do Qigong exercises or yoga. Use technology and social media to maintain fitness levels.[4]

Elderly with advancing age will have a more challenging time to reverse the effects of deconditioning of the musculoskeletal system. Children and adolescents have higher physical activity needs than adults, and the quarantine period makes this need tougher to achieve. Cardiorespiratory exercise should be done for 150 minutes of moderate-vigorous intensity or 75 min of vigorous-intensity per week, or a combination of both, and also moderate to high-intensity muscle-strengthening activity. This can be achieved even at home, with no special equipment and limited space.[6]

Tips To Stay Active At Home

It would be best if you took active short breaks by standing up and walking around every 30 minutes when you sit or watch television. Try not to sit continuously for more than 1 hour. Performing domestic chores such as washing clothes, sweeping floor, or gardening can increase physical activity time. Light-intensity activities like mobilizing the muscular masses and the joints are fine. Older people can perform them even in sitting or semi-lying position.[6]

In this pandemic and social restriction era, there are a lot of online courses, and luckily some of them are free. Follow the online courses, exercise videos, or play with your children, such as playing hide and seek. Avoid screen time while playing with children in favor of playful activities and active playing. Fitness video games with motion sensors can be useful, especially for

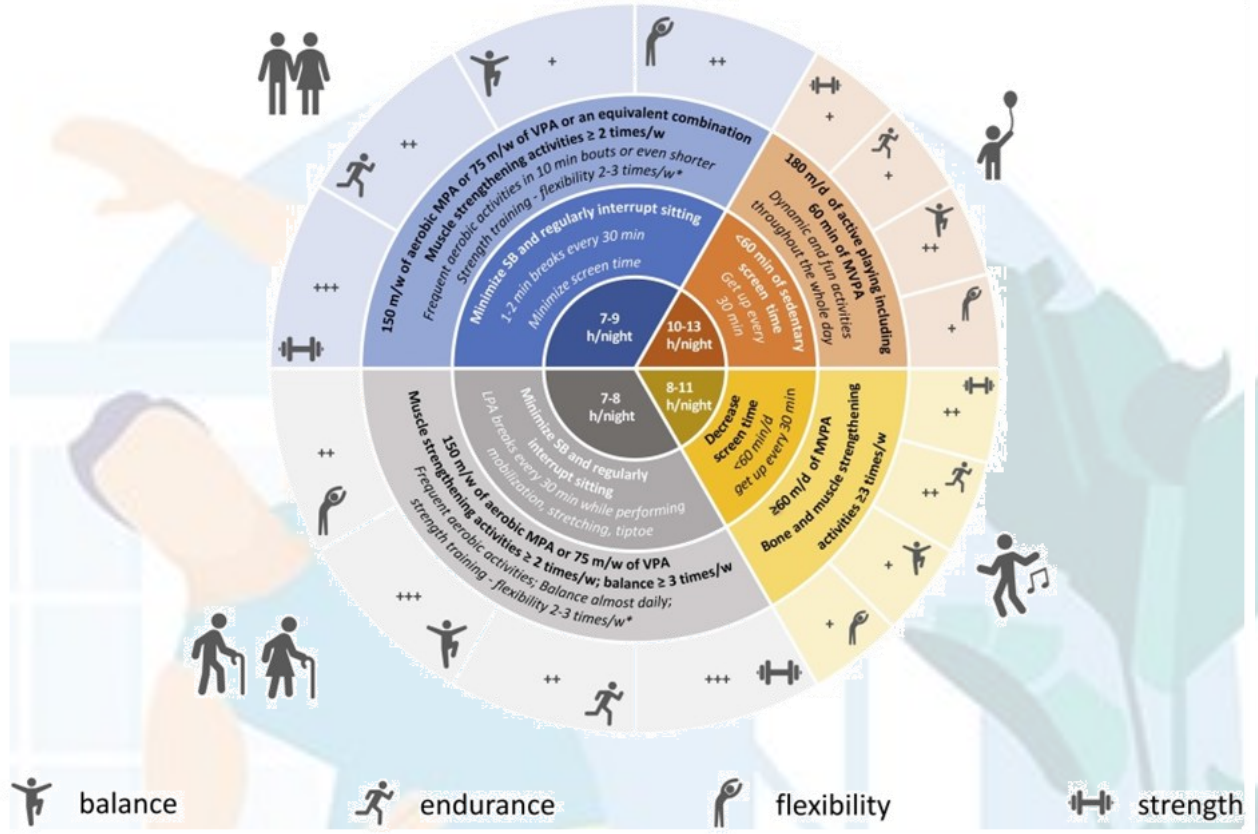

FIGURE 1 | Physical activity, sedentary behavior, sleep recommendations, and tips for COVID-19 quarantine period. Blue, adults; gray, older people; orange, pre-schooler; yellow, school-aged children and adolescents; Bold, international guidelines and recommendations; Italic, tips for quarantine period; PA, physical activity; SB, sedentary behavior; LPA, light-intensity physical activity; MPA, moderate-intensity physical activity; VPA, vigorous-intensity physical activity; MVPA, moderate to vigorous-intensity physical activity. In the central portion of the figure, we reported recommended hours of sleep by age group. *Perform strengthening activities in non-consecutive days. +, ++, + + +: relative importance of PA/exercise type for each age category. Dumbbell: muscle and bone-strengthening activities; running: aerobic activities; monopodalic standing: balance exercise; bending: flexibility.[6]

children and teens. Performing these activities protects you from sedentariness. Active play rather than screen time helps you and your children to avoid snacking. [6]

Do positive things regularly, such as regular times for main meals, sleep, and exercise. Prioritize continuity and regularity instead and then gradually increase the frequency, duration, and intensity. Activity trackers and smartphone apps can help you to monitor your progress.[6]

For all of us, young and old, regular physical activity is vital for staying healthy. Don't just sit and sleep all day long while we are still in quarantine mode. Get up, do some exercise, play with your children, follow the exercise video, stretch your muscle, do moderate-intensity exercise, so you have a better immune function. This regular physical activity can also reduce your feelings of stress and anxiety. Fit in 2, 5, 10, or 20 minutes, however, and wherever you can. Every active minute counts![7]

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