# INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

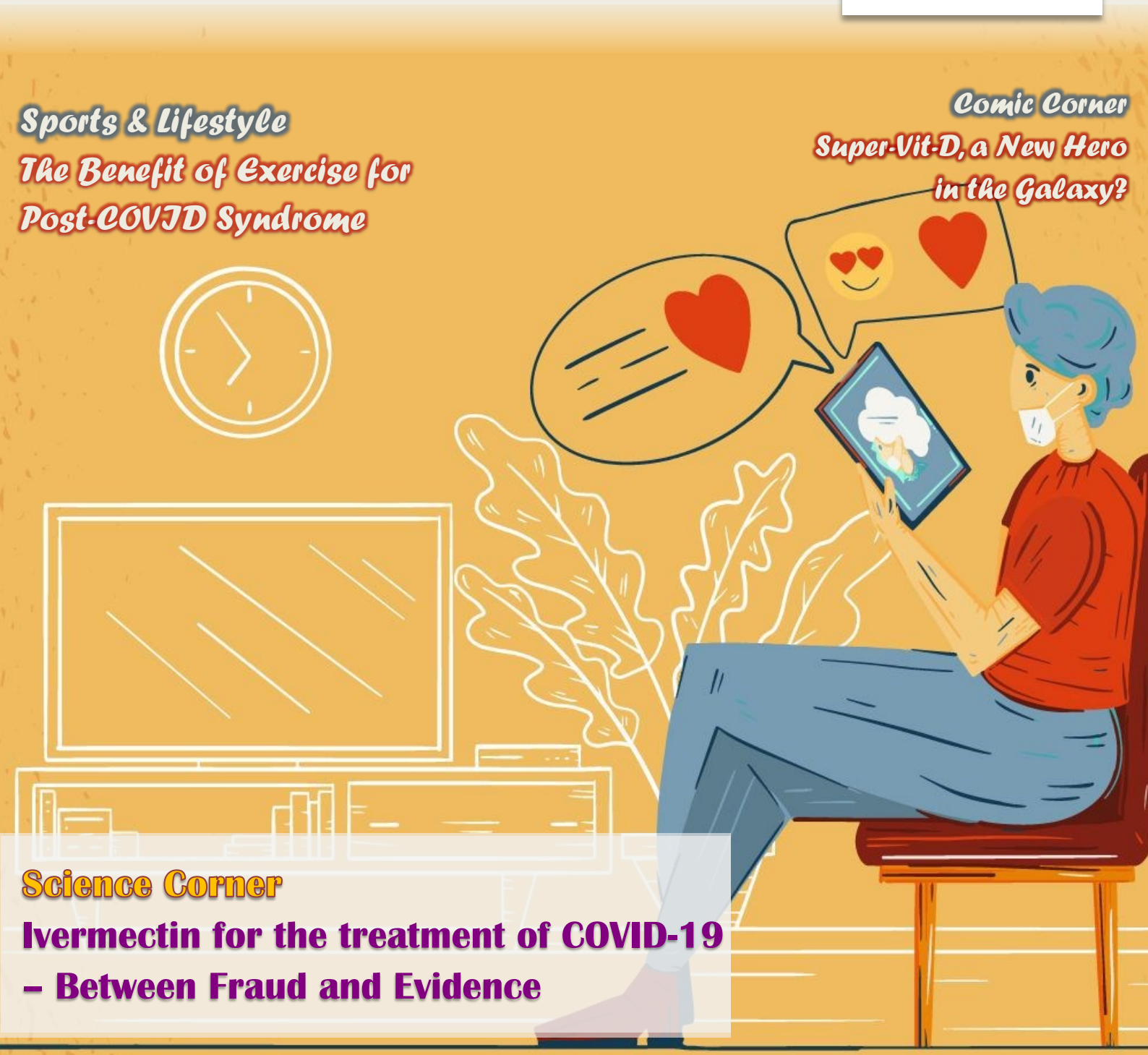
KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

July 2021

Sports & Lifestyle
The Benefit of Exercise for Post-COVID Syndrome

Comic Corner
Super-Vit-D, a New Hero in the Galaxy?



Science Corner
**Ivermectin for the treatment of COVID-19 – Between Fraud and Evidence**

NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2021

# INA-RESPOND newsletter

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## FEATURES

# INA-RESPOND Newsletter

## TRIPOD & PROACTIVE Study Updates

By: Eka Windari R., Lois E. Bang, Melinda Setiyaningrum, Retna Mustika Indah, Riza Danu Dewantara

STUDY UPDATES

### INA102

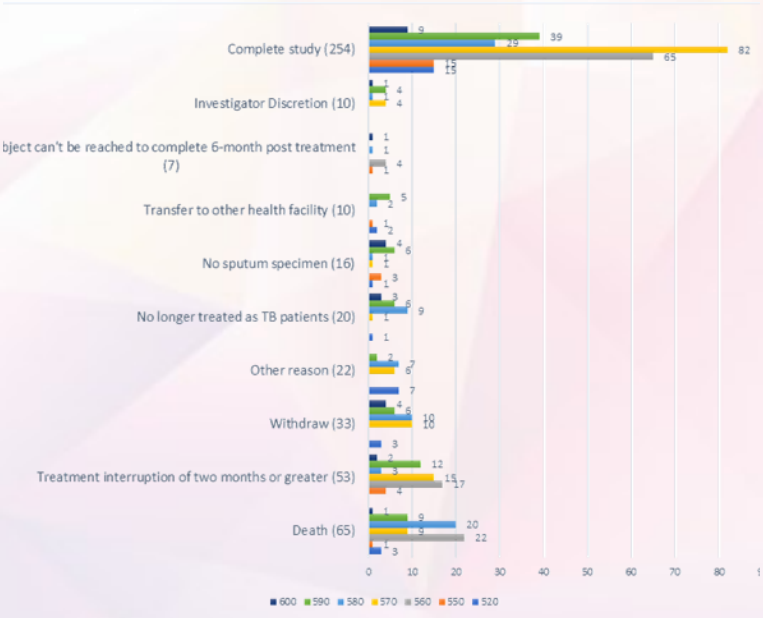
Per 06 May 2021, all the participants in the TRIPOD study have a study completed from 490 enrolled participants. Two hundred and fifty-four participants have completed the study, while 236 participants are terminated early (including death). From the uploaded CRFs, all participants from sites 520, 550, 560, 570, 580, 590, and 600 have completed the study. Sites 520, 550, 560, 570, 580, 590, and 600 have completed the upload of the Source Document Worksheet.

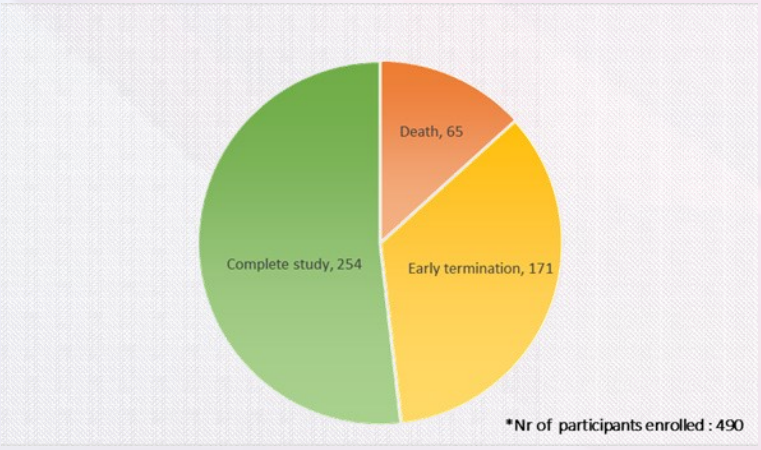
The database Quality assurance (except for TB Treatment pages) has been conducted for sites 520, 550, 560, 570, and 590. The Quality assurance of critical values for site 550 was conducted on 28-29 Apr 2021, and the quality assurance for subject random was conducted on 30 April - 23 May 2021.

The Site Close-out Visit (SCV) has been conducted for site 520 on 30 November – 1 December 2020, site 570 on 15-16 December 2020, site 590 on 19-20 January 2021, site 560 on 20-21 April 2021, and site 550 on 22-23 June 2021. All Site Close-out Visit (SCV) action items from sites 520, 570, 590, 560, and 550 are already resolved. The upcoming SCV will be conducted at site 600 on 21-22 July 2021 and site 580 on 24-25 August 2021. All essential documents, CRF, SDW, and laboratory test results are already available in the EDMS for all sites. The study documents from these sites will be archived in the IndoArsip for long-term archival at least five years after the study is closed.

The INA-RESPOND secretariat has announced an official letter and a final report on site closure to the hospital director and the local ethics commission. For sites 520, 570, 590, they were reported on 14-Apr 2021, and for site 560, they were reported on 18-May 2021. This procedure will be done for sites 550, 600, and 580 as soon as the SCV is completed at each site.

The TRIPOD isolate was sent to Central Laboratory in Padjajaran University Bandung on 12 April 2021 for the subculture. Subculture will be prepared for several tests regarding TB, including TB strain examinations which is one of the TRIPOD secondary objectives.




Per protocol, there are eight types of specimens collected on TRIPOD study for future use. Status for Repository specimens is provided in figure 4.

| Site | Site Closed Out Visit | Current Status/Awaiting Items |
|---|---|---|
| 520<br>(n=32) | Done,<br>30 November – 1 December 2020 | Study documents has been sent to Indo Arsip |
| 550<br>(n=25) | Done,<br>22-23 June 2021 | Final report has been finalized, the cover letter will need to be fully signed by Head of Centre Two, NIHRD.<br>Study document still being prepared by the local RA, then all of the study documentations will be sent to INA-RESPOND for inventory purpose. |
| 560<br>(n=108) | Done,<br>20-21 April 2021 | Study documents has been sent to Indo Arsip<br>DST result for 1 subject |
| 570<br>(n=128) | Done,<br>15-16 December 2020 | Study documents has been sent to Indo Arsip |
| 580<br>(n=83) | Planned,<br>24-25 Augusts 2021 | SCV preparation but not limited to QA Process by DM, File Review by CRSS and Specimen Management Review by CRA |
| 590<br>(n=89) | Done,<br>19-20 January 2021 | Study documents has been sent to Indo Arsip |
| 600<br>(n=25) | Planned,<br>21-22 July 2021 | SCV preparation but not limited to QA Process by DM, File Review by CRSS and Specimen Management Review by CRA |

| Site | Specimen Type | Whole blood (EDTA) - DNA | Whole blood (Heparin) - PBMCs | Whole blood (Heparin) – Plasma | Whole blood (PAXgene) - RNA | Urine | Saliva | Sputum | MTB Isolate |
|---|---|---|---|---|---|---|---|---|---|
| **520 (n=32)** | **BL (32)** | 90 | 22 | 91 | 27 | 125 | 62 | 19 | 36 |
| | **M1 (24)** | NA | 18 | 64 | 21 | 99 | NA | 16 | 12 |
| | **M2 (24)** | NA | 22 | 68 | 24 | 93 | NA | 11 | 0 |
| | **EOT (15)** | NA | 28 | 45 | 15 | 60 | 30 | 2 | 0 |
| **560 (n=108)** | **BL (108)** | 382 | 204 | 328 | 102 | 440 | 216 | 131 | 272 |
| | **M1 (95)** | NA | 188 | 285 | 94 | 381 | NA | 107 | 60 |
| | **M2 (87)** | NA | 172 | 261 | 86 | 348 | NA | 91 | 20 |
| | **EOT (73)** | NA | 142 | 219 | 73 | 292 | 146 | 75 | 19 |
| **570 (n=128)** | **BL (128)** | 438 | 177 | 380 | 121 | 519 | 254 | 119 | 192 |
| | **M1 (104)** | NA | 162 | 311 | 103 | 416 | NA | 43 | 92 |
| | **M2 (97)** | NA | 162 | 294 | 98 | 392 | NA | 22 | 38 |
| | **EOT (80)** | NA | 162 | 243 | 81 | 320 | 160 | 4 | 12 |
| **580 (n=83)** | **BL (83)** | 235 | 130 | 210 | 67 | 308 | 147 | 26 | 42 |
| | **M1 (44)** | NA | 70 | 102 | 38 | 156 | NA | 18 | 6 |
| | **M2 (38)** | NA | 54 | 81 | 36 | 148 | NA | 16 | 0 |
| | **EOT (29)** | NA | 50 | 71 | 27 | 124 | 61 | 8 | 0 |
| **590 (n=89)** | **BL (89)** | 340 | 170 | 255 | 84 | 344 | 147 | 78 | 55 |
| | **M1 (59)** | NA | 98 | 147 | 49 | 196 | NA | 17 | 8 |
| | **M2 (56)** | NA | 80 | 120 | 41 | 164 | NA | 8 | 0 |
| | **EOT (40)** | NA | 46 | 72 | 24 | 96 | 46 | 9 | 0 |
| **600 (n=25)** | **BL (25)** | 100 | 50 | 75 | 25 | 100 | 50 | 50 | 30 |
| | **M1 (13)** | NA | 26 | 39 | 13 | 52 | NA | 26 | 4 |
| | **M2 (11)** | NA | 22 | 33 | 11 | 44 | NA | 22 | 4 |
| | **EOT (9)** | NA | 20 | 30 | 10 | 40 | 20 | 20 | 0 |
| **550 (n=25)** | **BL (25)** | 95 | 48 | 72 | 24 | 100 | 51 | 10 | 27 |
| | **M1 (20)** | NA | 36 | 54 | 19 | 68 | NA | 7 | 7 |
| | **M2 (20)** | NA | 36 | 54 | 17 | 72 | NA | 6 | 4 |
| | **EOT (15)** | NA | 26 | 39 | 13 | 52 | 25 | 0 | 2 |

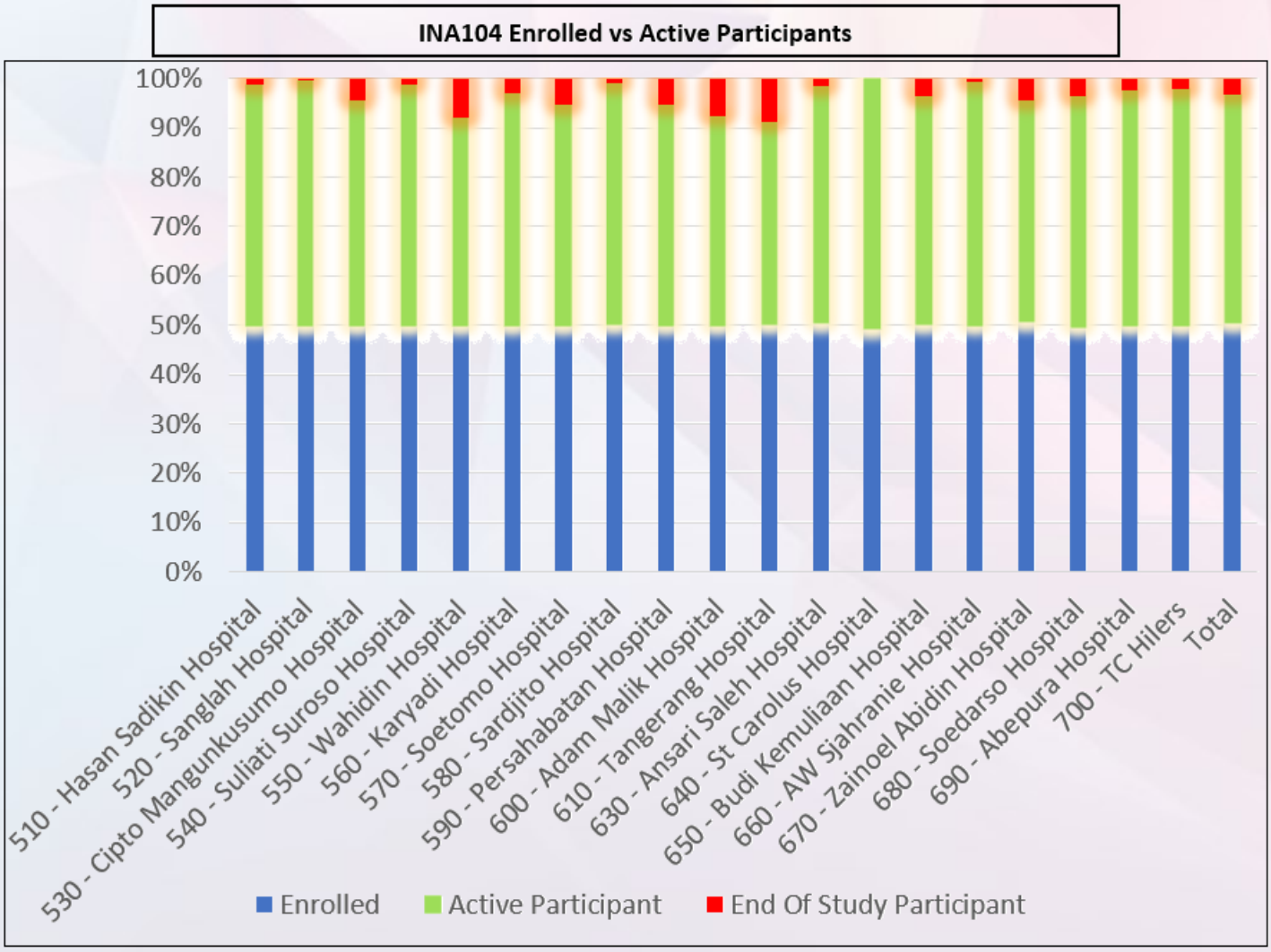
*Figure 4. Repository Specimens and Aliquots per Jul 2021*

## INA104

Based on the data on 08 July 2021, from 4,336 subjects enrolled, 285 subjects have finished their participation in the study due to some reasons: 176 subjects died, 23 subjects moved away to the city where site PROACTIVE is not available, 25 subjects withdrew, 5 subjects had negative HIV test result, and 114 subjects completed the last Follow Up Month 36; 14 subjects at Site 530 (Cipto Mangunkusumo Hospital), 31 subjects at Site 550 (Wahidin Sudirohusodo Hospital), 1 subject from Site 570 (Soetomo Hospital), 30 subjects at Site 600 (Adam Malik Hospital, Medan) and 36 subjects at Site 610 (Tangerang Hospital), 1 subject at Site 650 (Budi Kemuliaan Hospital), and 1 subject at Site 630 (Ansari Saleh Hospital),

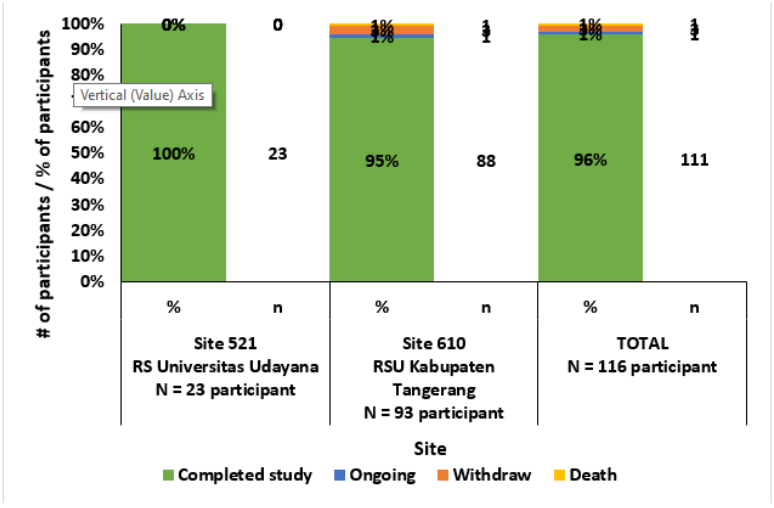
Below is the Chart of Enrolled and Active Participants by Sites:

Meanwhile, Onsite SMV (Site Monitoring Visit) was conducted to Site 570 (Soetomo Hospital) on May 3-5 and remote SMV conducted to Site 610 (Tangerang Hospital) on May 6-7.

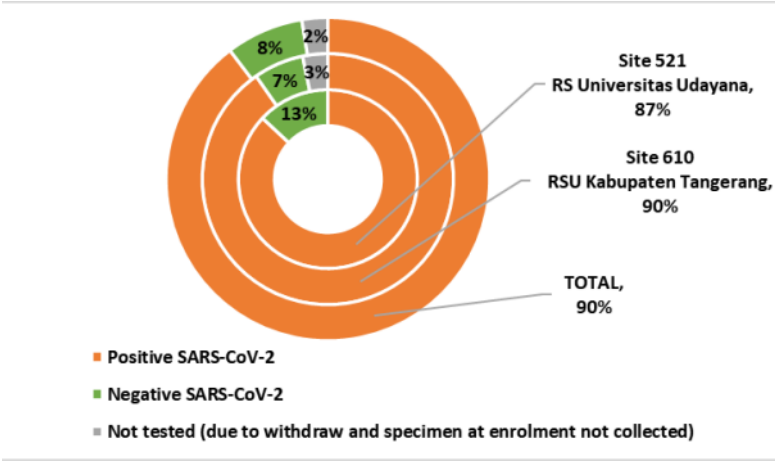


## INA107

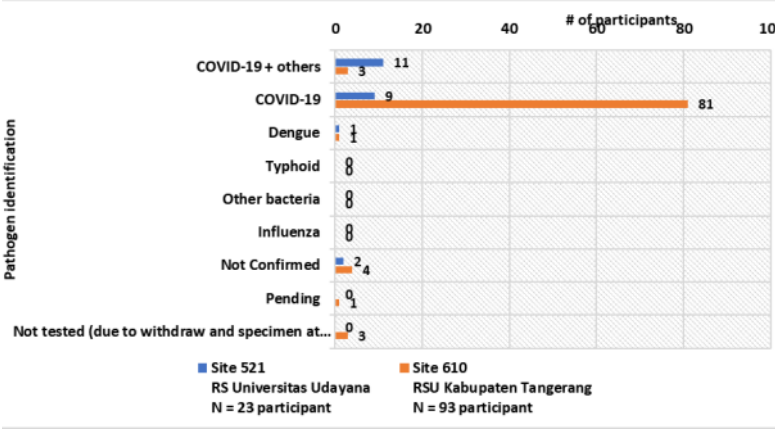
Based on the uploaded CRFs on 08 July 2021, 116 participants were enrolled in the ORCHID study, which consisted of 93 participants from site 610 (RSU Kabupaten Tangerang, Tangerang) and 23 participants from site 521 (RS Universitas Udayana, Denpasar). There were 111 participants (96%) who already completed this study, 1 participant passed away during the study, 1 participant was still ongoing with the study, and 3 participants withdrew (figure 1).




Up to 08 July 2021, 104 participants (90%) were identified as SARS-CoV-2 positive, and only 9 participants (7%) were identified as SARS-CoV-2 negative. Three participants were not tested due to withdrawal. At site 610, the number of participants identified as SARS-CoV-2 positive was 84 participants (90%), 6 participants as SARS-CoV-2 negative, and 3 participants were not tested due to withdrawal. While in site 521 there were 20 participants (87%) identified as SARS-CoV-2 positive and 3 participants (13%) identified as SARS-CoV-2 negative (figure 2).




Based on pathogen identification data, at site 521, 11 participants (48%) pathogen identified as COVID-19 with others, and 9 participants (39%) identified as COVID-19 only. While at site 610, 81 participants (87%) pathogen identified as COVID-19 only, following 3 participants (3%) identified as COVID-19 with others. Within 6 participants not confirmed for any pathogen, 2 participants at Site 521 and 4 participants at site 610. Only one participant identified a single infection of Dengue at both sites. An examination cannot be performed for 3 withdrawn participants (figure 3).




As of 09 July 2021, the ORCHID study team updated the Case Report Form (CRF) version 2.0 to version 3.0 to incorporate one additional log, Leftover SoC Specimen During Interim Visit. Along with the CRF update, CRF-Completion Guideline (CRF-CG), Source Document Worksheet (SDW), and annotated CRF were also updated.

There is an ongoing discussion with the NIAID team regarding budget re-allocation to the next financial year due to the adjustments of laboratory parameters and the number of subjects. In the meantime, the site is expected to increase the number of enrolments up to 4 subjects/week based on the site's capacity during the COVID-19 situation. The response letter to the central ethical committee review was discussed and submitted by the Secretariat and currently waiting for approval by the Ethics Committee.

INA-RESPOND
Newsletter

# IVERMECTIN FOR THE TREATMENT OF COVID-19 – BETWEEN FRAUD AND EVIDENCE

By: Yan Mardian

SCIENCE CORNER

The coronavirus disease 2019 (COVID-19) pandemic continues to grow. Protective vaccines have been developed, but current supplies are too low to cover worldwide demand in the coming months. Researchers worldwide are urgently looking for interventions to prevent new infections, or prevent disease progression, and lessen disease severity for those already infected. While research on new therapeutic agents for COVID-19 is key, there is also great interest in evaluating the potential of already existing medicines against COVID-19, and many clinical trials are in progress to re-purpose drugs normally indicated for other diseases. The known safety profiles shortened development timelines, and well-established markets for most of the already existing compounds proposed for COVID-19 are particularly advantageous compared to new drug discovery in a pandemic situation. This situation has inspired multiple drug re-purposing screens to find antiviral therapeutics that can be rapidly used for that purpose. Biological plausibility, pathophysiological considerations, in vitro research, observational studies, and/or clinical trials with heterogeneous quality evaluated several re-purposed drugs different from their current indications1. To date, over 1,974 drugs and investigational drugs have been reported to have in vitro activity against SARS-CoV-2. Since almost all of these actions against human targets might be unlikely to be viable against a novel virus, the mechanism of action arises. However, some policymakers and regulatory institutions authorized emergency use of unproven COVID-19 treatments, in which the use of some of these treatments has been heavily politicized in some regions2.

As of July 2021, three re-purposed anti-inflammatory drugs have shown significant survival benefits: the corticosteroid dexamethasone and the Interleukin-6 (IL-6) receptor antagonist drugs; tocilizumab, and sarilumab. Those benefits had been shown on the large studies of the Randomized, embedded, multifactorial, adaptive platform trial for community-acquired pneumonia (REMAP-CAP) trial and the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, in which those drugs are mainly indicated to treat severe/critical COVID-19 patients to suppress inflammation that can worsen the patient's condition3,4. Besides the anti-inflammatory drugs, the US Food and Drug Administration (FDA) has also issued an Emergency Use Authorization (EUA) for the anti-SARS-CoV-2 monoclonal antibody (Bamlanivimab plus etesevimab, or Casirivimab plus imdevimab, or Sotrovimab) for the treatment of non-hospitalized patients with mild to moderate COVID-19 who are at high risk of progression to severe COVID-195. However, other re-purposed drugs with potential antiviral mechanisms such as hydroxychloroquine, lopinavir/ritonavir, remdesivir, and interferon-beta, have shown no significant survival benefit in two large, randomized trials despite initial reports of efficacy on in-vitro or small-scale studies6–8. These facts show that currently, there is no single antiviral drug that has a strongly proven ability to inhibit SARS-CoV-2 replication, underscoring the need for caution when interpreting early clinical trial data.

One candidate for drug therapy of SARS-CoV-2 infection that has attracted the attention of researchers worldwide is Ivermectin (IVM), which is a well-established anti-parasitic drug used worldwide for a broad number of parasites (including head lice, scabies, river blindness (onchocerciasis), strongyloidiasis, trichuriasis, ascariasis, and lymphatic filariasis) and proved to be safe at the conventional dose of ≤200 μg/kg, although severe adverse effects ranging from ataxia to seizures have occasionally been reported9. It may also be applied as a cream to control the common inflammatory skin condition papulopustular rosacea. But IVM is most used for veterinary parasitic diseases, especially gastrointestinal worm infestations. Consequently, it is readily available and relatively inexpensive. In the intervening years, the effectiveness of ivermectin and its derivatives in treating parasitic worm infections transformed human and veterinary medicine, leading to a Nobel Prize for its discoverers, William C Campbell and Satoshi Ömura (https://www.nobelprize.org/prizes/medicine/2015/press-release/).

IVM was first developed in the 1970s from a bacterium in a soil sample collected from woods alongside a Japanese golf course in Kawana. This drug is a semisynthetic derivative product from the fermentation product released by bacteria in the soil (Streptomyces acermitilis), further purified and isolated under the name avermectins10,11. This compound has been investigated to have antiparasitic activity by selectively binding and open inhibitory glutamate-gated chloride ion channels at the junction between nerve and muscle cells of the nematode par-

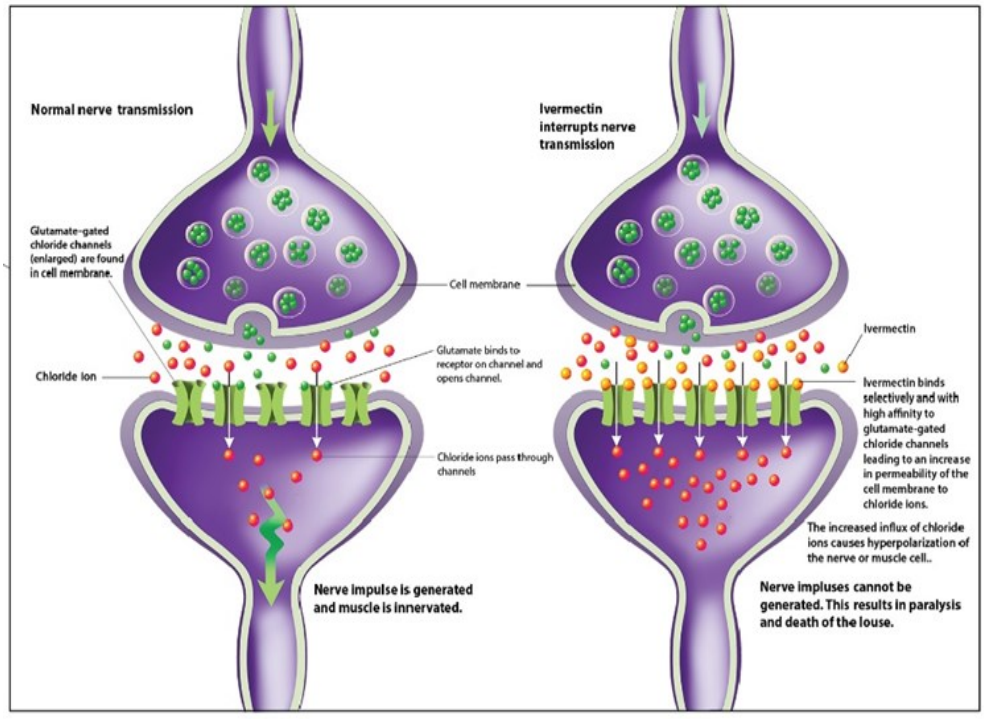



**Figure 1.** Mechanism of Action of Ivermectin as Antiparasitic
Source: Roche et al, *J Clin Exp Dermatol Res*, 2021

asite, causing hyperpolarization and paralysis death of the parasite (Figure 1)10,11. In addition, IVM prevents the filarial ability to release inhibitors of the host immune response. In tissue cultures, at concentrations higher than anthelmintic concentrations, IVM showed antiviral (e.g., dengue), antiparasitic (e.g., malaria), and anticancer (e.g., epithelial ovarian cancer) effects. However, these in vitro results have not been clinically demonstrated12,13.

In March 2020, researchers from Australia showed IVM activity against SARS-CoV-2 in cell cultures through experiments on Vero/hSLAM cells inoculated with SARS-CoV-2 (Australian isolate/VIC01/2020). After 48 hours of observation, the investigators observed a 5000-fold (99.8%) decrease in viral RNA concentration in Ivermectin-treated samples compared with controls (Figure 2)14. However, concentrations required to inhibit viral replication in-vitro (EC50=2.2 - 2.8µM; EC90=4.4µM) were equivalent to more than 50 until 100-fold the normal Cmax achieved with a standard single dose of IVM 200 µg/kg, raising concerns about the efficacious dose of IVM for treating or preventing SARS-CoV-2 infection in humans and its tolerability15,16. In addition, even though IVM appears to accumulate in the lung tissue (2.67 times that of plasma), but this is also unlikely to be sufficient to maintain target concentrations for pulmonary antiviral activity. IVM doses with such high concentrations have never been used in any clinical trials and are very likely to induce drug toxicity effects17. However, EC50 results can vary greatly depending on lab methodology, cell lineage, viral quantification methods, the strain of the virus cultured, and the multiplicity of infection used. Specifically, in SARS-CoV-2, EC50 for previously tested re-purposed drugs have varied significantly. For example, Remdesivir in-vitro study showed better performance >10 fold better in hACE2 augmented A549 cells (0.115 µM) than Vero E6 (1.28µM). Consequently, the EC50 demonstrated for ivermectin against SARS-CoV-2 should be interpreted with caution as it is unlikely to be one set value and liable to change depending on the lab18–20.

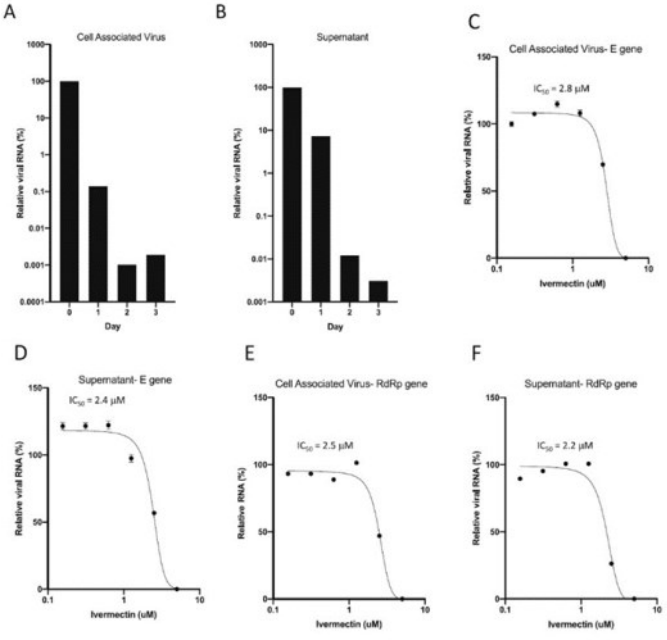



**Figure 2**. Ivermectin as a SARS-CoV-2 potent inhibitor shown on Vero/hSLAM cells.
Source: L. Caly, et al. Antiviral Research, 2020

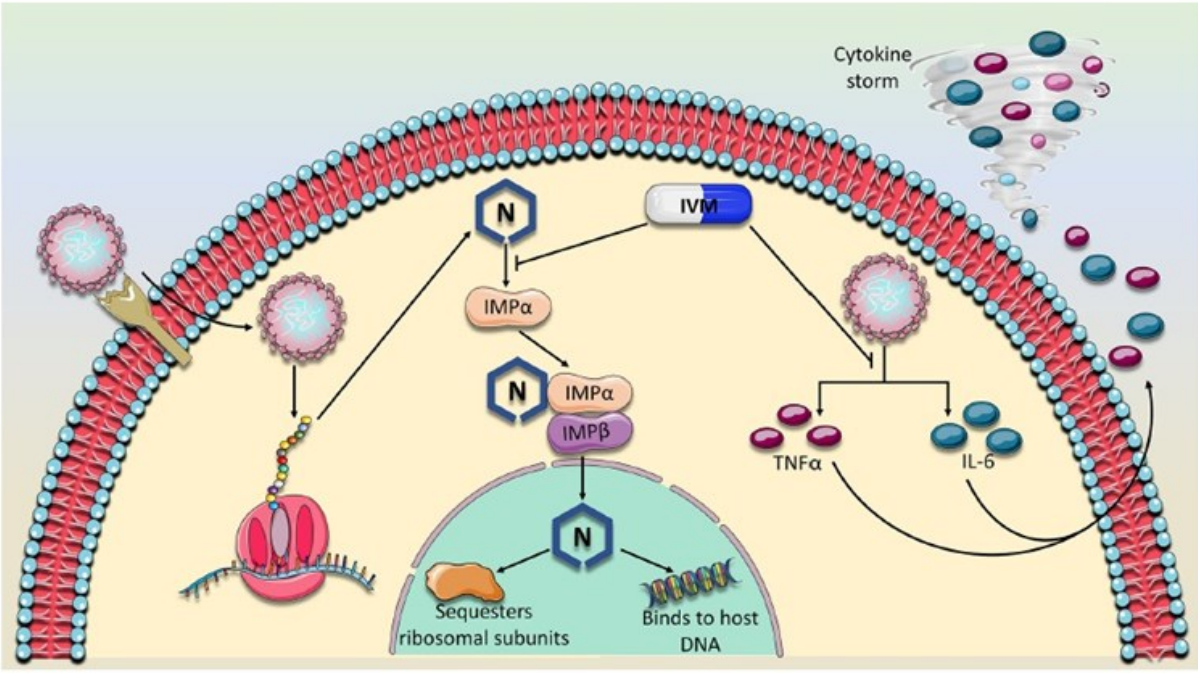



**FIGURE 2** | Proposed mechanism of action of Ivermectin against SARS-CoV-2. IVM has previously been established as a nuclear import inhibitor by binding to and antagonizing the ability of the importin (IMPα) to bind to its target cargo. Because the nucleocapsid (N) protein contains a nuclear localization signal, IVM is expected to prevent the binding of IMPα to the N binding site. Consequently, N would not perform its nuclear activity which is thought to suppress the host immune response and sequester ribosomal subunits, mechanisms which are thought to abrogate sufficient viral replication. In addition, the expression of two major cytokines, TNFα and IL-6 which drive the detrimental cytokine storm in COVID-19 patients were also shown to be dampened in the presence of IVM. As of yet, these two major mechanisms which involve viral replication and immune response suppression appear to characterize the main activities of IVM against SARS-CoV-2.

**Figure 3.** Proposed mechanism of action of Ivermectin against SARS-CoV-2.

IVM was shown to specifically inhibit the host cell importin (IMP)α/β1 mediated nuclear import required for replication of HIV-1 and Dengue virus, and therefore it was proposed as the potential mechanism by which it inhibits SARS-CoV-2. Furthermore, because the nucleocapsid (N) protein of SARS-CoV-2 contains a nuclear localization signal, IVM is expected to prevent the binding of IMPα to the N binding site, which is a likely mechanism that contributes to IVM's ability to hinder SARS-CoV-2 in vitro replication. Consequently, N would not perform its nuclear activity, which is thought to suppress the host immune response and sequester ribosomal subunits, mechanisms that are thought to abrogate sufficient viral replication. However, the fundamental function of the N protein is to package the viral genome RNA into a long helical ribonucleocapsid (RNP) complex and participate in the assembly of the virion through its interactions with the viral genome and membrane protein in the host cytoplasm, the well-established and main site for SARS -CoV-2 replication to occur. Thus, yet to say, it is still premature to presume N protein import function to host cell nucleus in the SARS-CoV-2 life cycle. Some studies also mentioned that the expression of two major cytokines, TNFα and IL-6, which drive the detrimental cytokine storm in COVID-19 patients, were also shown to be dampened in the presence of IVM. In an in-vivo study, subcutaneous administration of ivermectin 400 μg/kg did not affect SARS-CoV-2 viral loads in hamsters. However, there was a reduction in olfactory deficit (measured using a food-finding test) and reduced interleukin (IL)-6:IL-10 ratio in lung tissues. Thus, despite controversial hypothesis, these two major mechanisms, which involve viral replication and immune response suppression, appear to characterize the main activities of IVM against SARS-CoV-2 (Figure 3)21,22.

Nevertheless, despite controversial doses and unclear mechanism of action against SARS-CoV-2, assessments of IVM as prophylaxis or treatment for mild to severe COVID-19 continue being published in peer-reviewed journals or have been made available as manuscripts ahead of peer review (preprints) and protocol repositories. Some clinical studies showed no benefits or worsening of the disease after IVM use. In contrast, others reported a shorter time to resolution of disease, greater reduction in inflammatory marker levels, shorter time to viral clearance, or lower mortality rates in patients who received IVM than in patients who received comparator drugs or placebo. However, most of these studies had small sample sizes, incomplete

information, and yet methodologically limited by heterogeneity in the population receiving IVM, doses applied, and uncontrolled cointerventions, making it difficult to exclude common causes of bias (https://www.covid19treatmentguidelines.nih.gov/). Just recently, one of the largest and most promising studies showing IVM as COVID-19 treatment has withdrawn over ethical concerns. The preprint study on the efficacy and safety of IVM in treating COVID-19, led by Dr. Ahmed Elgazzar from Benha University in Egypt, was published on the Research Square website in November 2020. It is claimed to represent the results of a multi-center, 600-patient randomized control trial (RCT) study evaluating IVM use in preventing and treating COVID-19. Despite never passing peer-review or being published in any scientific journal, the Elgazzar study went on to get cited in approximately 30 other studies, including two meta-analyses. Since the Elgazzar study is so large and so massively positive – showing a 90% reduction in mortality, a substantial effect in preventing the onset of the disease and significantly reduced inflammatory markers compared to control – it hugely skews the evidence in favor of IVM of those meta-analyses. A medical student in London, Jack Lawrence, was among the first to identify serious concerns about the paper, leading to the retraction. He found the introduction section of the paper appeared to have been almost entirely plagiarised. The data also looked suspicious, with the raw data apparently contradicting the study protocol on several occasions, and some data seems to be fabricated (https://www.theguardian.com/science/2021/jul/16/huge-study-supporting-ivermectin-as-covid-treatment-withdrawn-over-ethical-concerns).

On different websites (such as https://ivmmeta.com/, https://c19ivermectin.com/, or https://tratamientotemprano.org/estudiosivermectina/), which conducted meta-analyses of IVM studies, they showed unpublished colorful forest plots which rapidly gained public acknowledgment and were disseminated via social media, without following any methodological or report guidelines. These websites do not include protocol registration with methods, search strategies, inclusion criteria, quality assessment of the

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with control | Risk with ivermectin | | | |
| All-cause mortality follow up: range 5 days to 28 days | 6 per 100 | **2 per 100** (1 to 7) | **RR 0.37** (0.12 to 1.13) | 787 (5 RCTs) | ⨁◯◯◯ VERY LOW [a,b] |
| Length of stay follow up: range 5 days to 28 days | The mean length of Stay was **10** days | **MD 0.72 days more** (0.86 fewer to 2.29 more) | - | 286 (3 RCTs) | ⨁◯◯◯ VERY LOW [c,d] |
| Adverse events follow up: range 5 days to 28 days | 76 per 100 | **72 per 100** (65 to 81) | **RR 0.95** (0.85 to 1.07) | 467 (3 RCTs) | ⨁⨁◯◯ LOW [e] |
| Severe adverse events follow up: range 5 days to 28 days | 0 per 100 | **0 per 100** (0 to 0) | **RR 1.39** (0.36 to 5.30) | 179 (3 RCTs) | ⨁⨁◯◯ LOW [f] |
| Viral clearance follow up: range 5 days to 28 days | 410 per 1,000 | **394 per 1,000** (312 to 472) | **RR 0.96** (0.76 to 1.15) | 262 (4 RCTs) | ⨁⨁◯◯ LOW [g] |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; MD: Mean difference
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Table 1.** Summary of findings table of the effect of ivermectin compared to standard of care or placebo for COVID-19 patients

included studies, nor the certainty of the evidence of the pooled estimates. Prospective registration of systematic reviews with or without meta-analysis protocol is a key feature for transparency in the review process and ensuring protection against reporting biases by revealing differences between the methods or outcomes reported in the published review and those planned in the registered protocol. These websites show pooled estimates suggesting significant benefits with IVM, which has confused clinicians, patients, and even decision-makers. This is usually a problem when performing meta-analyses that are not based on rigorous systematic reviews, often leading to spurious or fallacious findings16.

One large RCT, which included 476 patients, was published in March 2021 in JAMA. This study showed no effect of ivermectin on the duration of symptoms of adults with mild COVID-19. The authors stated that the findings did not support the use of ivermectin in these patients, but again highlighted that larger trials were needed to determine whether the drug had other benefits23. In addition, in a recently published meta-analysis analyzing ten RCTs, excluding Elgazzar study, IVM did not reduce primary outcomes (all-cause mortality, length of hospital stay, and adverse events) or secondary outcomes (SARS-CoV-2 clearance in respiratory samples and severe adverse events) RCTs of patients with mostly mild COVID-19 disease. The quality of evidence was low or very low for all outcomes and at high risk of bias (Table 1)24.

On its living guideline, the WHO recommends not using ivermectin in patients with COVID-19 except in the context of a clinical trial (https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.2). This recommendation applies to patients with any disease severity and any duration of symptoms. The WHO panel observed the effects of IVM on mortality, mechanical ventilation, hospital admission, duration of hospitalization, and viral clearance remain uncertain because of very low certainty of evidence addressing each of these outcomes. Evidence was rated as very low certainty primarily because of very serious imprecision for most outcomes: the aggregate data had wide confidence intervals and/or very few events. There were also serious concerns related to the risk of bias for some outcomes, specifically lack of blinding, lack of trial pre-registration, and lack of outcome reporting for one trial that did not report mechanical ventilation despite pre-specifying it in their protocol (publication bias). In comparison, the US-NIH stated in their COVID-19 Treatment Guidelines Panel that there is still insufficient data for the Panel to either recommend or against the use of IVM to treat COVID-19 (https://www.covid19treatmentguidelines.nih.gov/). The results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19 are urgently awaited.

In conclusion, despite promising effects observed on the in-vitro study and inexpensive nature of the drug, currently available studies reporting the effect of IVM as an option of COVID-19 re-purposed drug have serious methodological limitations with very low certainty of the evidence. Furthermore, as explained above, fraud research widely cited in favor of IVM therapy for COVID-19 has been recently withdrawn. Therefore, the use of IVM for both prophylaxis or treatment of COVID-19 should be done based on trustable evidence, without conflicts of interest, with proven safety and efficacy patient-consented, ethically approved, RCT studies. Nevertheless, it would therefore be premature to conclude absolutely that ivermectin has no place in COVID-19 treatment. However, on the basis of current evidence, its use cannot be recommended to treat COVID-19 patients and should only be used within clinical trials context.

REFERENCES:


1. Prats-Uribe A, Sena AG, Lai LYH, et al. Use of repurposed and adjuvant drugs in hospital patients with covid-19: multinational network cohort study. BMJ. 2021;373:n1038. doi:10.1136/bmj.n1038
2. Tummino TA, Rezelj V V, Fischer B, et al. Drug-induced phospholipidosis confounds drug re-purposing for SARS-CoV-2. Science (80- ). Published online 2021.
3. The REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021;384(16):1491-1502. doi:10.1056/NEJMoa2100433
4. Group RC. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693-704.
5. Taylor PC, Adams AC, Hufford MM, de la Torre I, Winthrop K, Gottlieb RL. Neutralizing monoclonal antibodies for treatment of COVID-19. Nat Rev Immunol. 2021;21(6):382-393. doi:10.1038/s41577-021-00542-x
6. WHO Solidarity Trial Consortium. Re-purposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. N Engl J Med. 2020;384(6):497-511. doi:10.1056/NEJMoa2023184
7. Organization WH. Therapeutics and COVID-19: Living Guideline, 31 March 2021. World Health Organization; 2021.

8. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Final Report. N Engl J Med. 2020;383(19):1813-1826. doi:10.1056/NEJMoa2007764

9. González Canga A, Sahagún Prieto AM, Diez Liébana MJ, Fernández Martínez N, Sierra Vega M, García Vieitez JJ. The pharmacokinetics and interactions of ivermectin in humans--a mini-review. AAPS J. 2008;10(1):42-46. doi:10.1208/s12248-007-9000-9

10. Guo J, Ma R, Su B, Li Y, Zhang J, Fang J. Raising the avermectins production in Streptomyces avermitilis by utilizing nanosecond pulsed electric fields (nsPEFs). Sci Rep. 2016;6(1):25949. doi:10.1038/srep25949

11. Roche D, O'Connor C, Murphy M. Ivermectin in Dermatology: why it 'mite' be useless against COVID-19. Clin Exp Dermatol. 2021;n/a(n/a). doi:https://doi.org/10.1111/ced.14704

12. Mastrangelo E, Pezzullo M, De Burghgraeve T, et al. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. J Antimicrob Chemother. 2012;67(8):1884-1894. doi:10.1093/jac/dks147

13. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem J. 2012;443(3):851-856. doi:10.1042/BJ20120150

14. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020;178:104787. doi:https://doi.org/10.1016/j.antiviral.2020.104787

15. Peña-Silva R, Duffull SB, Steer AC, Jaramillo-Rincon SX, Gwee A, Zhu X. Pharmacokinetic considerations on the repurposing of ivermectin for treatment of COVID-19. Br J Clin Pharmacol. 2021;87(3):1589-1590. doi:https://doi.org/10.1111/bcp.14476

16. Garegnani LI, Madrid E, Meza N. Misleading clinical evidence and systematic reviews on ivermectin for COVID-19. BMJ Evidence-Based Med. Published online April 22, 2021:bmjebm-2021-111678. doi:10.1136/bmjebm-2021-111678

17. Schmith VD, Zhou J, Lohmer LRL. The approved dose of ivermectin alone is not the ideal dose for the treatment of COVID-19. Clin Pharmacol Ther. 2020;108(4):762-765.

18. Hill A, Garratt A, Levi J, et al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. Open Forum Infect Dis. Published online July 6, 2021. doi:10.1093/ofid/ofab358

19. Xie X, Muruato AE, Zhang X, et al. A nanoluciferase SARS-CoV-2 for rapid neutralization testing and screening of anti-infective drugs for COVID-19. Nat Commun. 2020;11(1):1-11.

20. Abed Y, Baz M, Boivin G. Impact of neuraminidase mutations conferring influenza resistance to neuraminidase inhibitors in the N1 and N2 genetic backgrounds. Antivir Ther. 2006;11(8):971.

21. Zaidi AK, Dehgani-Mobaraki P. The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article. J Antibiot (Tokyo). Published online 2021:1-13.

22. Wehbe Z, Wehbe M, Iratni R, et al. Re-purposing Ivermectin for COVID-19: Molecular Aspects and Therapeutic Possibilities . Front Immunol . 2021;12:1040. https://www.frontiersin.org/article/10.3389/fimmu.2021.663586

23. López-Medina E, López P, Hurtado IC, et al. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. Jama. 2021;325(14):1426-1435.

24. Roman YM, Burela PA, Pasupuleti V, Piscoya A, Vidal JE, Hernandez A V. Ivermectin for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials. Clin Infect Dis. Published online June 28, 2021. doi:10.1093/cid/ciab591

INA-RESPOND Newsletter

FROM OUR PARTNER

# INTRODUCING DFDISCOVER AND DFCOLLECT (FROM DFNET)

By: Michael Duvenhage

Formerly known as DataFax, DFdiscover is a mature 21 CFR Part 11-compliant Clinical Data Management System (CDMS). The system has evolved over 28+ years of continuous development to address every phase's needs, size, and complexity of clinical trials or research projects.

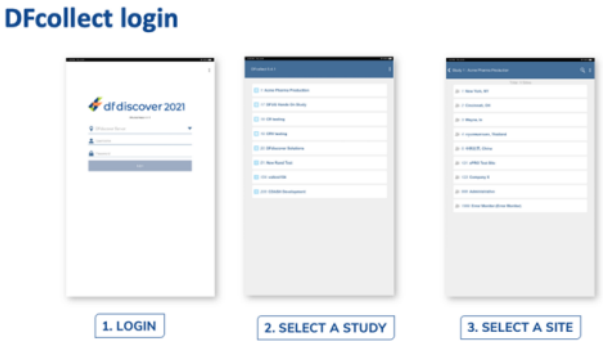
DFnet eClinical solutions consist of a variety of desktop apps and other data collection tools to collect and manage data from clinical trials.

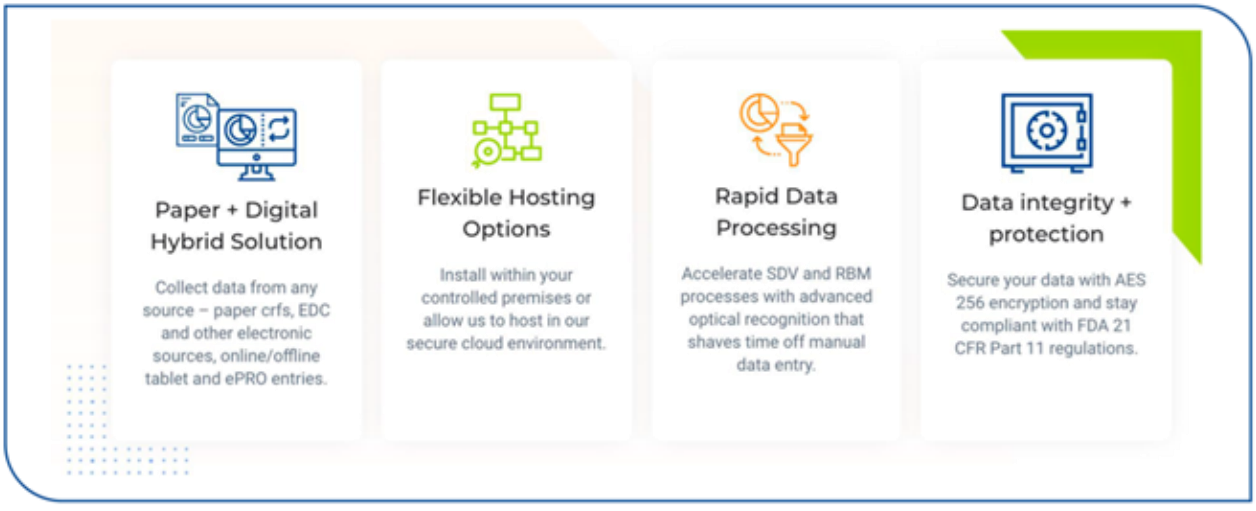

DFdiscover offers a flexible, highly customizable, hybrid solution with the ability to seamlessly transition between EDC, traditional paper CRFs, online/offline tablet data, and ePRO applications to meet protocol-specific and clinical research needs.

DFdiscover highlights include paper and digital (EDC) hybrid solutions, flexible hosting options, rapid data processing, and compliance to 21 CFR Part 11 regulations.

More recently, DFnet has released its DFcollect solution. DFcollect is a tablet-based application used to enter, review, and modify participant data. DFcollect allows for the online as well as offline data collection and is available for both iOS and Android products.

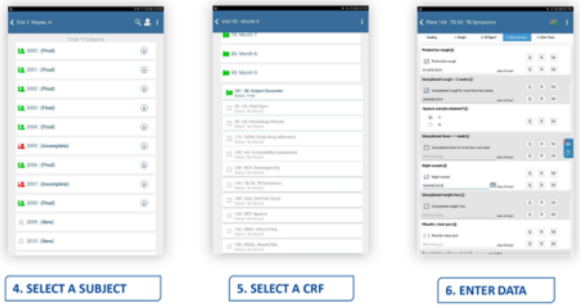
DFcollect application allows for the easy login (using usernames and passwords) into the DFdiscover database. Data access is provided on a study and site basis to authorized users only.



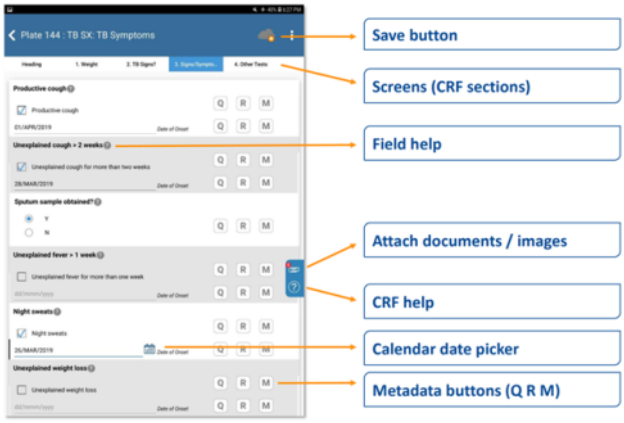



Navigation and data entry is managed through interactive screens within the DFcollect application.

## DFcollect data entry

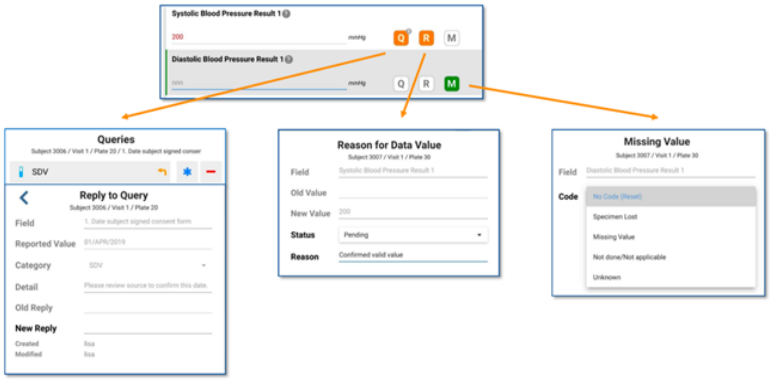



DFdiscover data entry screens are represented in a user friendly and intuitive manner within the DFcollect application allowing for the easy capture and management of clinical trial data.

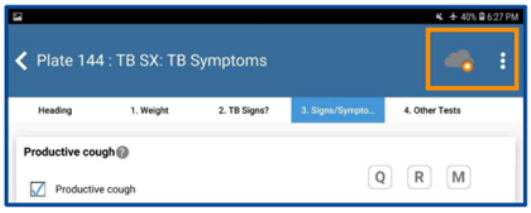


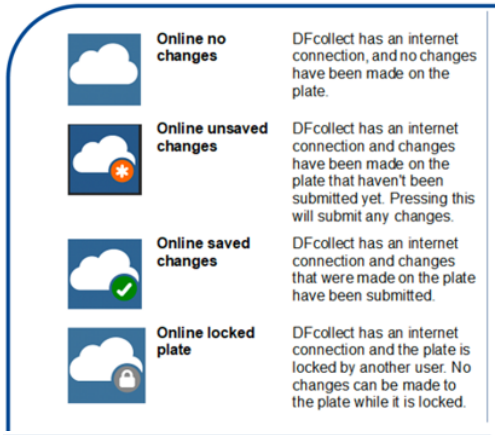

DFcollect further allows for the use of other metadata and functions, like data queries, data reasons, as well as representation of missing data values, allowing the easy management and cleaning of clinical trial data.

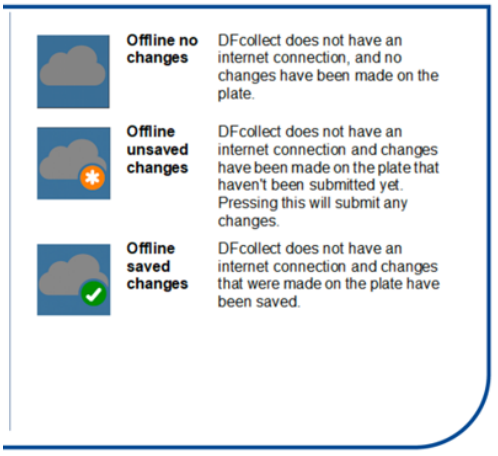
## Metadata: Queries, reasons, and missing values




Lastly, DFcollect allows for the capturing of clinical data in online as well as offline mode. This allows your clinical team to seamlessly work in remote locations or in areas not covered by data connections and sync data back to the DFdiscover server when data connection is available again.



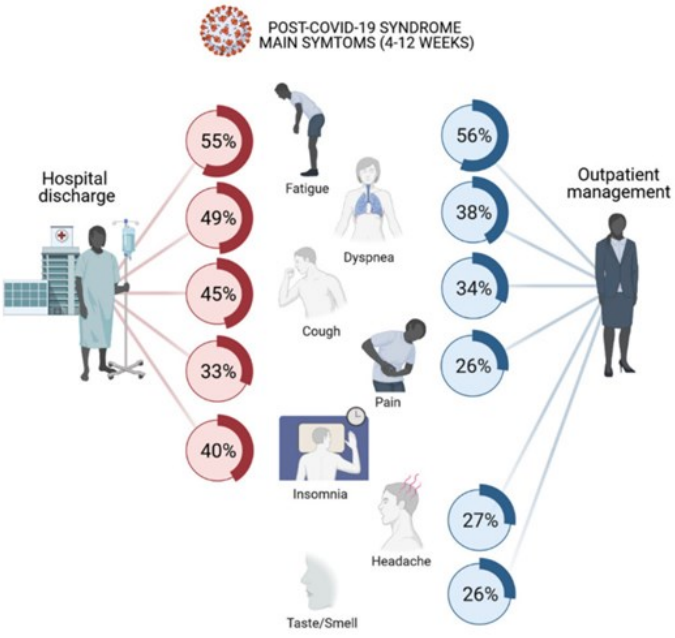
INA-RESPOND Newsletter

# THE BENEFIT OF EXERCISE FOR POST-COVID SYNDROME

By: Septi Mandala Putra

SPORTS & LIFESTYLE

Post-COVID syndrome is recognized as a new clinical entity in the context of SARS-CoV-2 infection with persistent symptoms more than three weeks after the diagnosis of COVID-19. It ranges from 10–35%1. The most common post-COVID symptoms are fatigue, dyspnea, olfactory and gustatory malfunction, chest pain, myalgia, and mental sleep disorders. It is estimated 10–35% of patients that do not require hospitalization may develop post-COVID symptoms, regardless of co-morbidities2




According University of Cincinnati Medical Centre for COVID-19, there are five categories of long COVID-19 syndrome, based on symptoms, time of onset and duration:3

Type 1: patients with varying duration of recovery that directly relates to the severity of acute infection, organ complications, and underlying medical conditions

Type 2: symptoms that persist six weeks from the onset of illness

Type 3: show periods of quiescence/near recovery, followed by a recurrence of symptoms persisting at least

⇒ 3A: Three months

⇒ 3B: Six Months

Type 4: Patients who are initially asymptomatic at the time of positive SARS-COV-2 test but become symptomatic

⇒ 4A: One to three months

⇒ 4B: At least three months later

Type 5: Patients who are asymptomatic / have few symptoms at the time of diagnosis and die within the next 12 months

The pathogenesis of post-COVID syndrome remains largely unknown. Evidence suggests that prolonged inflammation has a key role in the pathogenesis of most post-COVID manifestations.

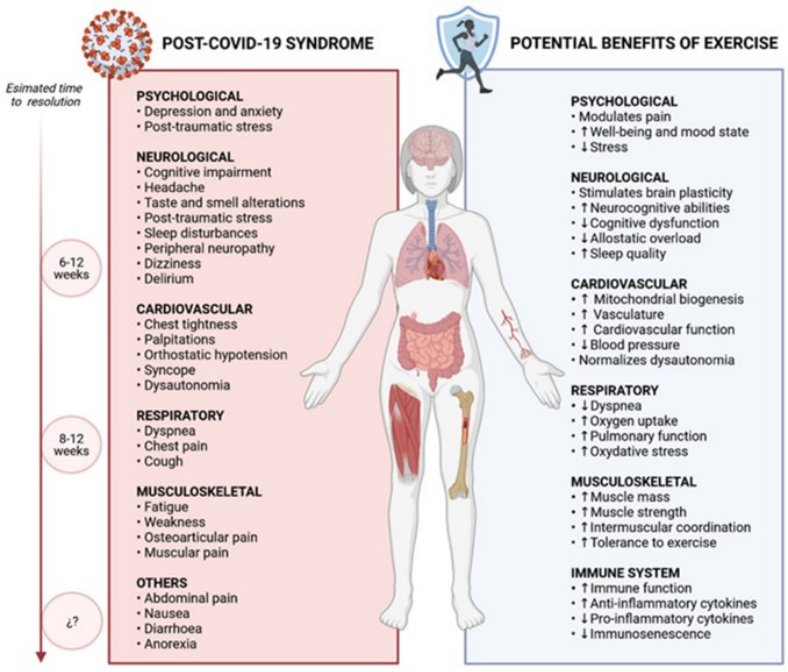
Beyond inflammation, post-COVID fatigue may be attributed to lung dysfunction. A prospective observational three-month follow-up study of 76 patients (mean age: 41.3 years) found that serum troponin-I levels during acute illness were significantly associated with the onset of fatigue after discharge4.

To date, there is still no specific treatment for the management of patients with the post-COVID-19 syndrome. The greatest research effort has rightly focused on preventing and treating the acute phase of the disease. Future research focusing on medical and social aspects must consider the disease continuum, including prolonged forms.

The COVID-19 syndemic is a situation generated by the convergence of infectious disease, the presence of other chronic non-communicable diseases, such as obesity, and the existence of social determinants, which affect the health of the population. The confinement, the subsequent perimeter closures of the cities and the limitation of urban mobility along with the cessation of all types of group activities, the interruption of non-professional team sports, and many other recreational options related to movements, such as parks and leisure areas or swimming pools, have further deteriorated the condition of citizens.

After the confinement, there has been a supposed return to normality, in which, on many occasions, previous activities have not been recovered, especially in people who have suffered COVID-19.

Therefore, it is necessary to recover physical exercise in the




inactive population and position it as a tool in the management of patients with the post-COVID-19 syndrome. Given that exercise has been shown to be beneficial in multiple pathologies with which the post-COVID-19 syndrome shares similarities both in terms of symptoms and its possible pathogenic mechanisms, it is worth considering the potentially favorable effect that this would bring in the recovery of these patients. Picture 2 explains the potential benefits of exercise on the symptoms of post-COVID syndrome.

Contrary to traditional beliefs, exercise is not detrimental to immune competency but rather can act as an adjuvant to stimulate the immune system by inducing mitochondrial adaptations, cell generation, and immune surveillance5. Physical fitness status can be a determining modifiable factor for the promotion of metabolic and functional adaptations in T lymphocytes and monocytes, counteracting inflammatory environments caused by sedentary behavior.

Individual and targeted exercise is highly recommended as a non-pharmacologic strategy for treating rheumatic and musculoskeletal diseases, characterized by chronic pain, muscle weakness, physical limitations, fatigue, and low tolerance to exercise6. Strength training and multicomponent exercise programs have been extensively demonstrated as safe and effective among vulnerable people in reversing frailty and weakness and restoring functional capacity in short- and long-term7.

Strength training support using low loads, low volume, and not-to-failure repetitions produce considerable improvements in maximal dynamic strength, power output, and muscle hypertrophy while preventing typical discomfort, fatigue, or stiffness after traditional high-demanding training8.

There is plenty of evidence that exercise is an essential therapeutic tool to improve cardiovascular health through enhancing mitochondrial biogenesis and function, restoring and improving vasculature (cardiac remodeling, angiogenesis, blood volume expansion), and the release of myokines from skeletal muscle that preserve or augment cardiovascular function10.

There is sufficient evidence suggesting that tailored and supervised exercise training may be an effective multisystemic therapy for the post-COVID-19 syndrome that suits the diversity of the cases and symptoms.

Further examination on the effects of exercise-based treatments on post-COVID-19 syndrome is required to give practical insights about what type of exercise should be preferably prescribed, with emphasis on intensity and load management and adherence strategies.

Reference

Maltezou, H. C., Pavli, A., & Tsakris, A. (2021). Post-COVID Syndrome: An Insight on Its Pathogenesis. Vaccines, 9(5), 497.

Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ. 2020 Aug

Becker R.C. COVID-19 and its sequelae: A platform for optimal patient care, discovery and training. J. Thromb. Thrombolysis. 2021:1–8.

Liang L., Yang B., Jiang N., Fu W., He X., Zhou Y., Ma W.L., Wang X. Three-month follow-up study of survivorsof Coronavirus Disease 2019 after discharge. J. Korean Med. Sci. 2020;35:e418.

Saçma M., Geiger H. Exercise generates immune cells in bone. Nat. Cell Biol. 2021;591:371–372

Peçanha T., Bannell D., Sieczkowska S.M., Goodson N., Roschel H., Sprung V.S., Low D.A. Effects of physical activity on vascular function in autoimmune rheumatic diseases: A systematic review and meta-analysis. Rheumatology. 2021

Valenzuela PL, Castillo-García A, Morales JS, Izquierdo M, Serra-Rexach JA, Santos-Lozano A, Lucia A. Physical Exercise in the Oldest Old. Compr Physiol. 2019 Sep 19;9(4):1281-1304.

Vieira AF, Umpierre D, Teodoro JL, Lisboa SC, Baroni BM, Izquierdo M, Cadore EL. Effects of Resistance Training Performed to Failure or Not to Failure on Muscle Strength, Hypertrophy, and Power Output: A Systematic Review With Meta-Analysis. J Strength Cond Res. 2021 Apr 1;35(4):1165-1175

Pinckard K, Baskin KK, Stanford KI. Effects of Exercise to Improve Cardiovascular Health. Front Cardiovasc Med. 2019 Jun 4;6:69.

INA-RESPOND Newsletter

# SUPER-VIT-D, A NEW HERO IN THE GALAXY?

By: Aly Diana

COMIC CORNER


Vitamin D (also referred to as "calciferol") is a fat-soluble vitamin that is naturally present in a few foods (mainly animal source foods), added to others (in fortified foods), and available as a dietary supplement. It is also produced endogenously when ultraviolet (UV) B rays from sunlight strike the skin and trigger vitamin D synthesis. Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal bone mineralization needed for bone growth and bone remodeling. Vitamin D has other roles in the body, including reduction of inflammation as well as modulation of such processes as cell growth, neuromuscular and immune function, and glucose metabolism. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D.

Lately, the popularity of vitamin D has increased due to some studies and the unproven hypothesis that 1) vitamin D deficiency increased the risk of COVID-19 infection; and 2) high dose vitamin D supplementation in hospitalized COVID-19 patients may reduce the severity

and improve outcomes. For the first hypothesis, the plausible explanations come from some studies that demonstrated that vitamin D deficiency was associated with acute viral respiratory tract infection, particularly caused by the influenza virus and acute lung injury.

Vitamin D generally reduces the risk of microbial infection and death by modulating innate and adaptive immunity and as a result of its antiviral and anti-inflammatory effects. Furthermore, vitamin D has a major impact in enhancing the expression of angiotensin-converting enzyme 2(ACE-2), which is an important receptor mediating the pathogenesis of SARS-CoV-2 infection. The pooled analysis in a systematic review and meta-analysis involving 14 studies showed that individuals with vitamin D deficiency were 80% more likely to acquire COVID-19 infection than those with sufficient Vitamin D levels (OR = 1.80; 95%CI: 1.72, 1.88). But more high-quality studies are needed.

For the second hypothesis; as we know, the severity of COVID-19 is determined by the presence of pneumonia, severe acute respiratory distress syndrome (SARS-CoV-2), myocarditis, microvascular thrombosis and/or cytokine storms, all of which involve underlying inflammation. A principal defense against uncontrolled inflammation and viral infection, in general, is provided by T regulatory lymphocytes (Tregs). Treg levels have been reported to be low in many COVID-19 patients and can be increased by vitamin D supplementation. Vitamin D deficiency is associated with an increase in thrombotic episodes, which are frequently observed in COVID-19. These conditions are reported to carry higher mortality in COVID-19. However, several literature reviews and meta-analyses until this moment have concluded that high doses of vitamin D supplementation in COVID-19 patients are not based on solid evidence. It still needs to await results from ongoing trials to determine the efficacy, desirable doses, and safety of vitamin D supplementation to prevent and treat COVID-19 related health outcomes.

Take home message: It is important to make sure that we have enough vitamin D (serum 25(OH)D) level in our body ($^{3}$50 nmol/L or $^{3}$20 ng/mL; and not more than 125 nmol/L or 50 ng/mL). Consuming a balanced diet is important. Please make sure that we have safe but enough sun exposure. Recommended dietary allowance for 1-70 years is 600 IU/day, and tolerable upper intake level for 9+ years is 4000 IU/day. Excess amounts of vitamin D are toxic. Because vitamin D increases calcium absorption in the gastrointestinal tract, vitamin D toxicity results in marked hypercalcemia, hypercalciuria, and high serum 25(OH)D levels. Hypercalcemia can lead to nausea, vomiting, muscle weakness, neuropsychiatric disturbances, pain, loss of appetite, dehydration, polyuria, excessive thirst, and kidney stones. In extreme cases, vitamin D toxicity causes renal failure, calcification of soft tissues throughout the body (including in coronary vessels and heart valves), cardiac arrhythmias, and even death.

Stay safe and keep healthy!

References:

Bassatne A, Basbous M, Chakhtoura M, El Zein O, Rahme M, El-Hajj Fuleihan G. The link between COVID-19 and VItamin D (VIVID): A systematic review and meta-analysis. Metabolism. 2021 Jun;119:154753.

Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010.

National Institute of Health. Vitamin D. https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/

Pereira M, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J. Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2020 Nov 4:1-9.

Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. Nutrients. 2013 Jul 5;5(7):2502-21. doi: 10.3390/nu5072502.

Stroehlein JK, Wallqvist J, Iannizzi C, Mikolajewska A, Metzendorf MI, Benstoem C, Meybohm P, Becker M, Skoetz N, Stegemann M, Piechotta V. Vitamin D supplementation for the treatment of COVID-19: a living systematic review.

Teshome A, Adane A, Girma B, Mekonnen ZA. The Impact of Vitamin D Level on COVID-19 Infection: Systematic Review and Meta-Analysis. Front Public Health. 2021 Mar 5;9:624559. doi: 10.3389/fpubh.2021.624559.

Wang Z, Joshi A, Leopold K, Jackson S, Christensen S, Nayfeh T, Mohammed K, Creo A, Tebben P, Kumar S. Association of vitamin D deficiency with COVID-19 infection severity: Systematic review and meta-analysis. Clin Endocrinol (Oxf). 2021 Jun 23. doi: 10.1111/cen.14540.

Weir EK, Thenappan T, Bhargava M, Chen Y. Does vitamin D deficiency increase the severity of COVID-19? Clin Med (Lond). 2020 Jul;20(4):e107-e108. doi: 10.7861/clinmed.2020-0301.

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# INA-RESPOND Newsletter

The Indonesia Research Partnership on Infectious Disease newsletter is an internal bulletin of INA-RESPOND research network intended to disseminate information related to the network's studies, activities, and interests to all members of the network as well as its sponsors and related parties.

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