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Newsletter

TRIPOD & PROACTIVE Study Updates

By: Eka Windari R., Lois E. Bang, Venty Muliana Sari, Melinda Setiyaningrum

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Per 19 Jan 2021, the TRIPOD study's total ongoing participants are 12 out of 490 enrolled participants. From those 12 ongoing participants, one is still on TB treatment while 11 are waiting for a 6-month post-treatment visit. Two hundred and forty-three participants have completed the study, while 235 participants are terminated early (including death). Therefore, there are still 2.45 % participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, all participants from sites 520, 570, and 590 have been completed the study. At the same time, there are 1 participant from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar) who still need to be followed up, 7 participants from site 560 (RSUP dr. Kariadi Semarang), 3 participants from site 580 (RSUP dr. Sardjito Jogjakarta), and 1 participant from site 600 (RSUP dr. Adam Malik Medan).

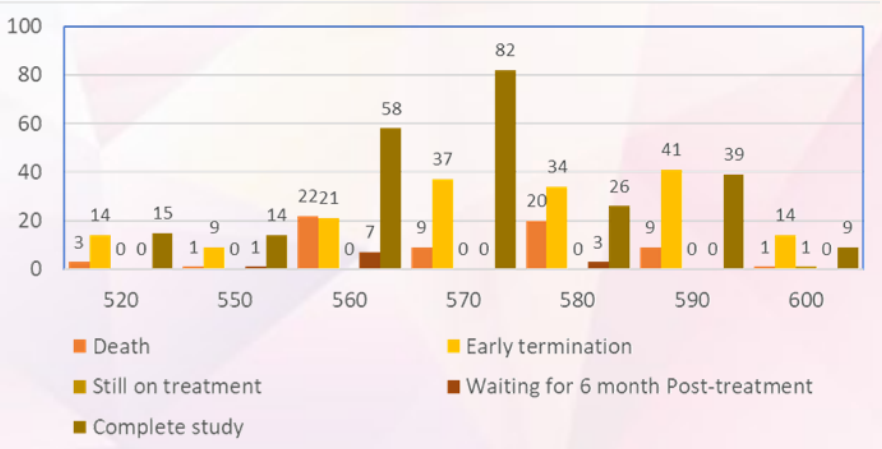


Figure 1. Participant status per site based on uploaded CRF per 19 January 2021

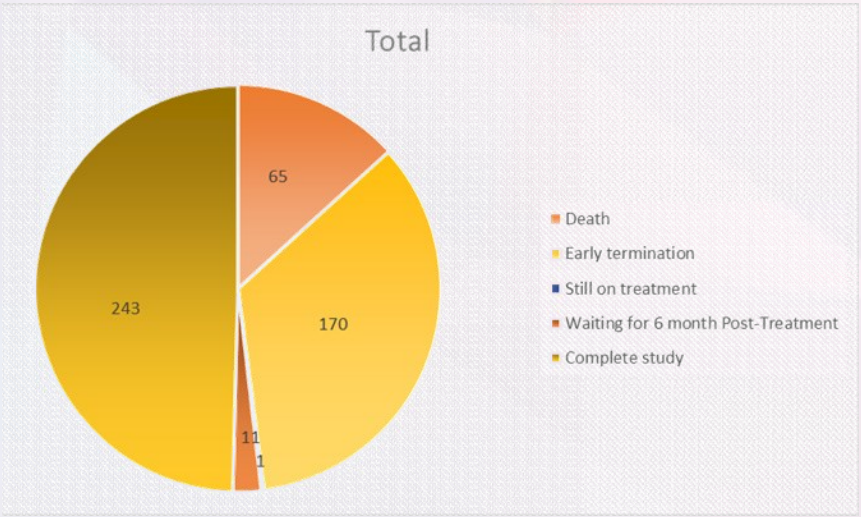


Figure 2. Total participant status based on uploaded CRF per 19 January 2021

The database Quality assurance (except for TB Treatment pages) was conducted for sites 520, 570, and 590 from 24 Nov – 22 Dec 2020.

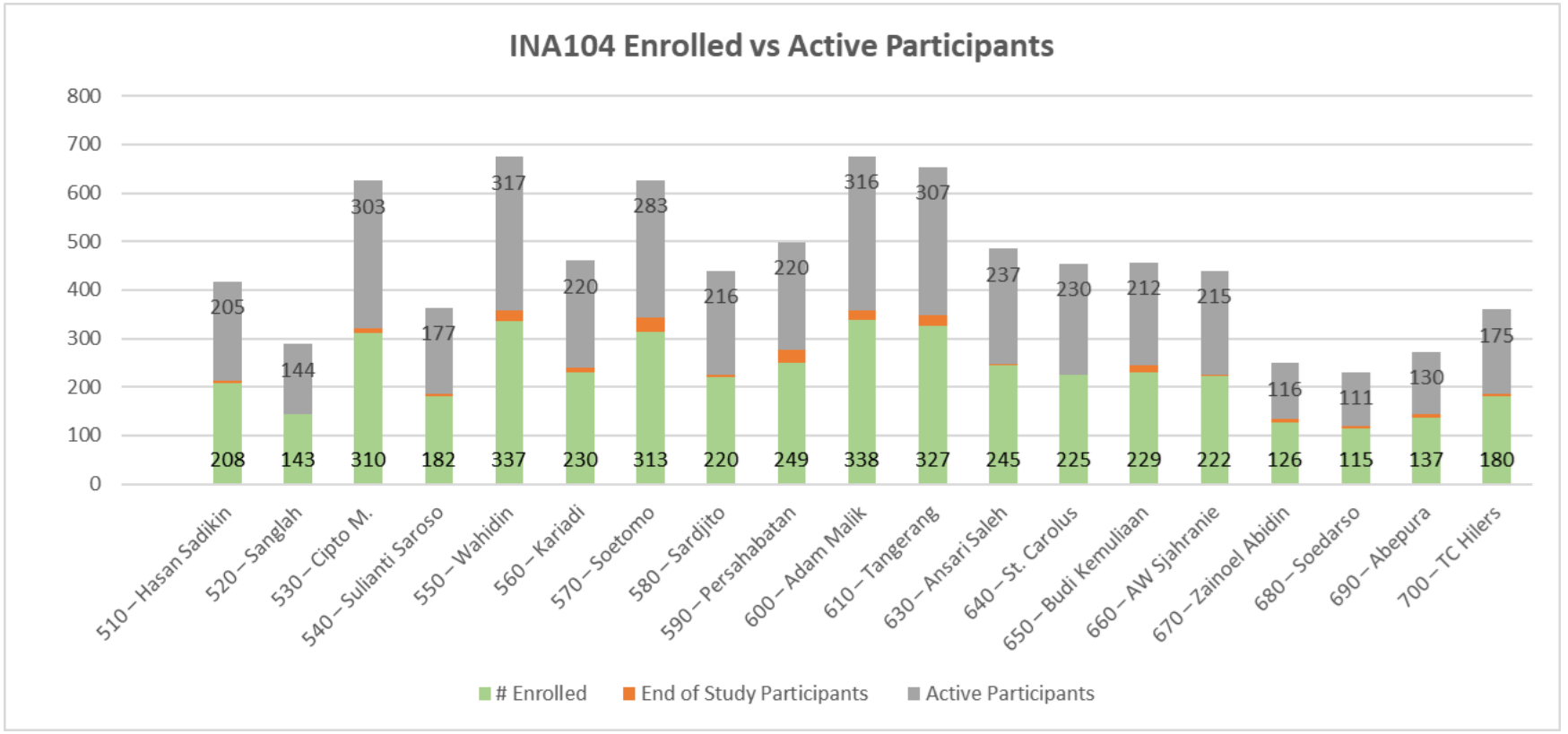
The Site Close-out Visit (SCV) was conducted for site 520 on 30 Nov – 1 Dec 2020, site 570 on 15-16 December 2020, and site 590 on 19-20 January 2021.

AWAITING CULTURE AND DST RESULT

The result for baseline culture and DST results from all sites are complete.

Three subjects from 2 sites have recently undergone the last Follow Up Month 36, one pediatric subject at Site 610 – Tangerang hospital and two adult subjects at Site 600 – Adam Malik Hospital, Medan, based on the latest data per 29 Jan 2021.

Whereas as of 12 Jan 2021, from 4,336 subjects enrolled, 202 subjects are End of Study for the following reasons: 154 subjects' death, 22 subjects move away to the city where sites PROACTIVE are not available, 21 subjects withdrew, and five subjects with negative HIV test result. To date, there are 4,134 active subjects in this study. Below is the Chart of Enrollment and Active Participants by Sites:



In January 2021, two Site Monitoring Visits (SMV) were done remotely. They are for site 630 – Ansari Saleh Hospital, Banjarmasin as the 4th SMV on 21-22 Jan 2021, and on 27 – 28 Jan 2021 for site 580 – Dr. Sardjito Hospital, Yogyakarta as the 4th SMV

INA-RESPOND Newsletter

CT VALUE IN SARS-COV-2 RT PCR TEST. HOW TO BEST INTERPRET IT?

By: Ungke Anton Jaya

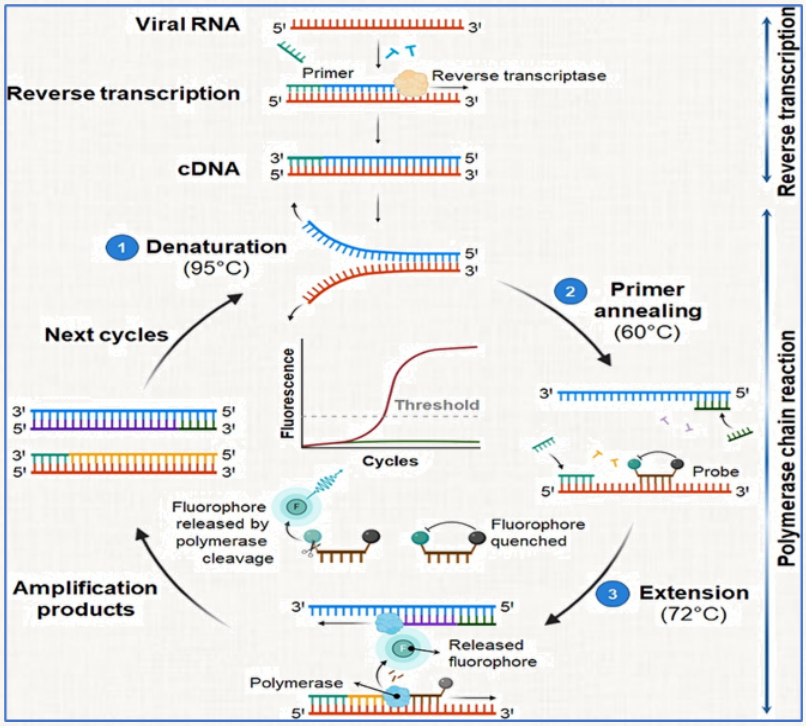
Background

Coronavirus pandemic cases reach 100 million cases and hit more than 219 countries around the world. The diseases are caused by the infection of the SARS-CoV-2 virus. The current standard method to diagnose COVID-19 infection is nucleic acid amplification test (NAAT) or molecular test to the presence of virus genome in the patient's samples. Two molecular test platforms are being used, the real-time RT-PCR(reverse transcriptase Polymerase chain reaction) and LAMP (Loop Mediated Isothermal Amplification) with RT-PCRas the most applied assay (WHO). The pandemic has hit many countries massively and fast, making the application of PCR diagnostic widely used by many laboratories. In Indonesia, at the beginning of the pandemic in early March 2020, only 12 laboratories were capable of conducting PCR assay for diagnosis of COVID-19, and now 612 laboratories have been approved by MOH to perform the PCR assay for COVID-19 diagnosis (Indonesia-MOH)

Realtime RT-PCR(Reverse Transcriptase Polymerase Chain Reaction) is the most common platform of PCR assay used. For this particular purpose, the assays are designed as a qualitative assay to give output as positive or SARS-CoV-2 genome detected or negative (not detected)

The basic principles of RT-PCR assay are the amplification of selected fragment/partial virus genome by the work of enzyme polymerase. The enzyme works through a series of reactions triggered by temperature changes in an instrument called thermocycler. The reactions are DNA denaturation from double strands to single strand, annealing of specific probe followed by the primer to the targeted fragment of the virus genome, and elongation of the attached primer to make a longer chain of DNA copy. Every time a new DNA strand is successfully formed, the probe will release a fluorescence signal that the intensity can be measured by an optical instrument. Once the reaction series is complete, the process is repeated again in the second cycle, and it keeps going until 40-45 cycles. During each cycle, the selected fragment target quantity is multiplied in double. The increase of DNA copy is detected by measuring the probe's signal intensity that is tagged to each DNA copy produced. The more number of cycles, the more copy of DNA produced, and the more signal is detected by the instruments and represented as logarithmic amplification curve projected against the cycles. At early cycles, the signal intensity will be very weak or undetected. DNA copies are doubled at every cycle following, giving a logarithmic increase of fluorescence signal intensity until the number of DNA copies produces a strong enough signal above the background signal or the threshold. That specific number of cycle determine the assay to call for positive result recognized as Cycle Threshold Value (CTV). The reaction will continue until the PCR chemical reaction condition slowly becomes not optimal anymore, making the cumulative amplification turn in to flat curve. If a high amount of virus genome presents in the swab samples, the CTV will be observed at the very early cycles (low CTV), while the little amount of virus genome will be detected at later cycles (high CTV). At the optimization stage, a serial dilution of the SARS-CoV-2 genome with a known quantity is applied as a template for RT-PCR assay to mimic the virus genome in the clinical sample. The effort can determine the last CTV that the assay can specifically detect the signal (cut off), and the lowest quantity of genome can be detected or limit of detection (LOD). Most commercial SARS-CoV-2 RT-PCR kits set the LOD limit 10-50 viral genome in the reaction and set the cut-off below CTV of 40. (picture 1).

The high and low CTV can give a rationale to correlate with and to estimate viral load in the samples. This is true. Many laboratories release the test result showing the CTV data. Unfortunately, interpreting CTV as a precise quantitative value for viral load estimation is not fully acceptable since the assay is designed to get qualitative output only, and the CTV varies between batch and kit. The accurate quantitative real-time PCR required a standardized template with a known quantity of viral genome run in the same assay with the clinical samples. Without proper background knowledge, the CTV result could confuse or even mislead the physician or patients. The article will explore how to best interpret CTV for diagnosis and correlation to the clinical condition.



Picture 1: A molecular representation of the real-time RT-PCRprinciple. The template (viral RNA) is converted to cDNA (complementary DNA) by reverse transcriptase (RNA dependent DNA polymerase enzyme). Subsequently, cDNA is amplified in a polymerase chain reaction (PCR) in three steps: (1) denaturation of cDNA at 95 _C, (2) annealing of the primers and probe

Factors influencing CTV

The real-time RT-PCR assay employs several components, primer and probe set, enzymes, buffer, the cycling condition, and the thermocycling instruments. The first components consist of forward primer, reverse primer, and probe. All are single strand short DNA of 20-25 bases with a sequence designed to complimentary match to the SARS-CoV-2 virus genome with high specificity. The primer will not be paired with other genomes from other microorganisms in the samples if any. The probe has a fluorescence label at one end. The primer and probe sequence is also designed to target the SARS-Cov-2 virus genome sequence with less or no variation (conserved area). Therefore, it can detect all circulating SARSCov-2 virus strains in the world. Most assays are designed using primer and probe to anneal at gene target E (envelope), RdRp (RNA dependent RNA polymerase), or N (nucleocapsid). To increase specificity and avoid false negative result, each assay uses a minimum of two amplification targets that could be separate fragments in the same gene (N1, N2) or two different genes target (WHO guideline). The second key component for the assay is the enzymes. The RT-PCR assay uses two enzymes, reverse transcriptase and DNA polymerase, with the complimentary buffer to ensure the optimal performance of enzyme activity. Each commercial kit uses its specific enzyme combination. The sequence of primers and probe and the enzyme's performance is the major factor to the sensitivity and specificity of the assay reflected in the CTV to determine the LOD and the cut-off. The same clinical sample is run in two different assays. Targeting different genes will give variation in CTV result similarly with two assays perform the assay using different RT-PCR kit employs different enzymes. Therefore, it is not reliable to compare the CTV from one assay to another assay and interpret it as an absolute number. A proficiency test conducted in Ontario, Canada, involving 26 laboratories that tested the same sample set gave variations up to 8 CTV. A study compared the sensitivity of five kits targeting various gene, N, E and RdRP gives variations of CTV with kit targeting N gene produce higher sensitivity reflected by lower CTV (Zhou et al – PLOs one) Public Health Ontario)

Naturally, real-time RT-PCR can be applied as a quantitative assay by using the standard of genomic template. The quantitative assay application adds more burden to the lab work, impractical, and does not necessary for diagnostic purposes since qualitative assay is considered sufficient. Quantitative real-time is vital during a study to evaluate disease progress or antiviral therapy.

In quantitative SARS-CoV-2 RT-PCR, dilution series of standardized genomic positive control with a known quantity is used in the assay. The standard control can be plasmid containing SARSCoV-2 genome, viral RNA, or virus culture with quantification unit stated as viral genome copies per 1000 cells in the respiratory swab, or per milliliter of serum sample or per gram stool sample. The clinical sample runs in the same batch as the standard. The CTV of the sample assayed can be extrapolated to a curve produced from CTV of genomic standard, and the genome quantity in the clinical sample can be calculated. Only a few studies have provided an indirect correlation between CTV to virus genome quantification in the sample. Han et al. conduct a comparison of three studies using different RT-PCR kits, all targeting the RdRp gene. The comparison can estimate at CTV 20-25, the sample contains more than 105 - 107 copies of the viral genome, at CTV 30-35, the viral genome is estimated at 102-104, and at CTV above, 35 less than 100 genome copies are detected. The accurate viral load quantification should only be determined at the actual assay with standard genomic applied.

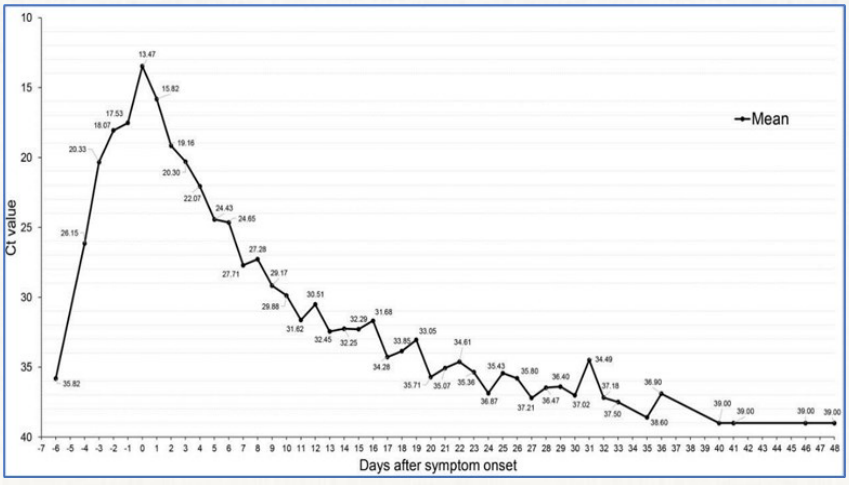
Duration of CTV detected in a patient sample

Several studies indicated that the virus detected in the clinical sample up to 5 days before symptom onset (Jang et al., Aaron et al.) and viral load reached its peak, indicate by highest CTV, on the onset of the symptoms and decrease after that, but the duration of the virus remain detected varies in many studies. A study in Wuhan indicated that CTV was detected up to 37 days with a median of 20 days after symptom of onset (Xi He nature medicine). Analysis from several studies indicate the median duration of virus detection from symptom onset using upper respiratory tract samples was 14.5 days, with the longest duration is 53.5 days) (Public Health Ontario).

There is an interesting cohort study following cases with one up to three recurrences of SARS-CoV-2 indicated by virus detected by RT-PCR assay. Unlike the first infection, at recurrence, the virus is detected at low CTV (between 35-40 by N1 gen PCR assay) or around cut off and detected up to 80 days after first onset (Huang et al.).

CTV and Infectivity --- PCR represent a live virus or could be just the trace

The molecular assay detects the virus genome in the specimen. The detected CTV for a long period of infection raises the question of whether the virus is still infective. An intact virus particle is required to allow a virus to infect the host cells. A study conducted in Germany followed nine patients with relatively mild cases. Clinical samples were taken daily and tested in parallel by two laboratories for RT-PCR and virus culture and assay to detect virus subgenomic mRNA. The viral RNA indicated by CTV remain detected for throat swab up to day 28 with an average of two weeks and up to three weeks for stool and sputum. From swab and sputum, viruses were grown from samples taken in the first week, but no virus was grown from samples taken after day eight. The virus subgenomic mRNA detected in the throat swab only up to day five indicated no or minimal virus replication after that. Viruses were not grown from stool despite the high viral load in the first week. (Wolfel et al.)



Picture 3. Changes in the SARS-CoV-2 Ct value of rRT-PCRin respiratory specimens. The calculated value as the mean of the Ct value of SARS-CoV-2 RNA(RdRP) in the nasopharyngeal specimens. The Ct value shows the lowest value on the day of symptoms and negative 3 weeks from the date of symptoms. (Negative > Ct value 35). (Picture credit to Jang et al.)

A study conducted in the US on 48 residents of a nursing facility involved pre-symptomatic, asymptomatic, and symptomatic cases with 13 days follow-up after symptom onset. The result showed from upper respiratory tract samples, the virus was isolated from samples with CTV range 13.6 to 34.3 (targeting N1 gene). The viable virus was isolated from samples collected between six days before to nine days after typical symptoms (fever, cough, and shortness of breath) and up to the last day of follow-up, 13 days, of the first evidence of any symptoms, including a typical one. (Arons et al.)

La Scola et al. followed up 155 patients and conducted rRT-PCR and virus culture to series of 183 nasopharyngeal samples. The virus was not grown from samples collected after day eight of symptom onset, despite ongoing high viral loads. Sample can be cultured only from samples with CTV ≥34 targeting the E gene. The authors inferred that patients with CT value ≥34 were no longer contagious and could be considered suitable for discharge (La Scola et al.).

A study attempted to isolate the virus from 90 confirmed positive samples by RT-PCR. The virus was grown in 26 samples (28.9%). All were from samples collected below eight days after symptoms or with CTV <24. (Bullard et al.).

A Study enrolls 100 patients in a public hospital in Singapore with mild to severe symptoms, including 12 (12%) with invasive mechanical ventilation. PCR was positive from nasopharyngeal swabs up to 48 days after symptom onset, with a mean duration of 16.7 days. No virus was isolated when the PCR cycle threshold (CT) value was >30 or >14 days after symptom onset, and no differences were observed in the duration of viral shedding stratified by disease severity (Young CID)

The detectable virus by PCR up to day 40-50 after onset but negative for virus isolation or subgenomic RNA after day 14 suggests that the virus is no longer viable, the virus is not intact, and only genomic trace is detected.

CTV and severity of the disease

The CTV reflects the amount of virus genome and can be correlated to the viral load in the clinical samples. The rationale to consider high viral load with more severe diseases the situation will give more exposure to the virus that in turn trigger extensive immune response. A study in 99 patients with moderately ill in Hubei, China, during the beginning of the pandemic showed no significant difference in CTV trend across age, sex group, or disease severity. In general, CTV was highest on the day of symptom onset. (He et al.). In a study in a group of nursing home residents in Washington with asymptomatic, pre-symptomatic, and atypical symptomatic with typical symptoms, the average CTV showed no significant difference with CTV 25.5, 23.2, 24.2, and 24.8, respectively. (Arons et al.)

Issues with real-time SARSCoV-2 PCR and how to best interpret CTV in a clinical setting

Variation of CTV between laboratories using different PCR kits targeting different kits is noticeable. Even when using the same kit and test at the same laboratories, variation between batch to batch variation is possible. In particular, if the specimen has a low viral load, meaning the quantity of template is low, the PCR efficiency will not be optimal anymore due to the uneven chances of primer and probe to pick up the genomic target. The low amount of template will give a wider CTV variation, usually at CTV above 35; the result could be inconsistent. Interpreting test result around cut-off, in most RT-PCR is usually at CTV below 40, is challenging. It is highly suggested to consider the result from earlier sample collection if available. Although the CTV can give the relative prediction of viral load in the samples, the absolute value cannot be naively compared from one laboratory to another laboratory. In general, the peak of CTV is during the first symptom onset and decrease within the first week but remain detectable for several weeks after it. The PCR result is not parallel with the virus culture and subgenomic mRNA as an indicator of virus capability to infect cells that are not detected after the second week.

The molecular test result can remain positive up to several weeks after onset, but the limited hospital capacity to hospitalize patients gives tension to release patients. It is reliable to consider US CDC recommendation to release patient 10-14 days after onset of symptoms or on two negative or close to CTV above 34 test at least 24 hours apart. (US CDC).

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INA-RESPOND Newsletter

COVID-19 VACCINES: PHASE 3 TRIALS AND BEYOND

By: Dr. Renee Ridzon

As the COVID-19 pandemic spread globally, it was recognized that effective vaccines were going to be essential to control viral transmission and decrease illness and death from SARS-CoV-2 infection. Vaccine development, which traditionally can take years or even decades, has been accelerated with the testing of multiple vaccine candidates in record-breaking time. This has been possible due to preexisting understanding based on studies of MERS and SARS and prior development of vaccine platforms. Currently, all potential COVID-19 vaccines have targeted the spike protein of the SARS-CoV-2 virus because it is immunogenic and effective blocking of the spike protein can block viral entry to the cell and prevent infection.

Phase 3 Vaccine Studies

Several different technologies have been utilized to produce COVID-19 vaccine candidates. The first vaccines that showed efficacy used mRNA technology, and studies of these vaccines produced by Moderna and Pfizer showed about 95% protection against symptomatic COVID-19 after two doses (Baden, Polack). Studies of three adenovirus vaccines have also been completed and have shown efficacy in the prevention of symptomatic infection ranging from 66%-91% (Vosey, Longunov, J&J press release). While still not reported in a peer-reviewed publication, the press release for one of these adenovirus vaccines led to a good bit of excitement as this vaccine is given in one rather than two doses. Preliminary results for the ongoing study of the protein subunit vaccine, Novavax, also demonstrate high efficacy (Novavax press release). Importantly, for all of these candidates, there is complete protection against severe disease and death. Taken together, this evidence gives us great reassurance that immunity elicited against the viral spike protein by different types of vaccines provides excellent protection from symptomatic infection and severe COVID-19. Because of design, the current length of follow-up, and other limitations, studies have been less clear on protection from asymptomatic infection and durability of infection. Also, because the current studies were conducted

only in adults, data on safety and efficacy in children has yet to be determined.

Efficacy versus Effectiveness

While phase 3 studies give data on efficacy in those who receive a vaccine, effectiveness in the context of broad implementation informs about the impact of a vaccine on population-based incidence of infection, and these data can only come after vaccine programs are initiated. With its early implementation of vaccination and its relatively small population, the country of Israel has provided important early observations about the real-world implementation of COVID-19 vaccination. By the end of January, one-third of the population of Israel was vaccinated with a first dose of the BNT162b2 (Pfizer) vaccine, and 19% had received both doses. At the time of scale-up of vaccination, there was a 66%-85% reduction in SARS-CoV-2-positive cases and over 90% reduction in severe hospitalizations, the first evidence of strong vaccine effectiveness (Aran).

Adverse Events with Vaccine Implementation

Clinical trials of COVID-19 vaccines carefully assessed products' safety; however, even the largest trials conducted in thousands of volunteers may not detect rare adverse events seen only when millions of doses are administered. With implementation of both mRNA vaccines, there have been several reports of anaphylaxis. In all cases, the reaction occurred within minutes after vaccine dosing and there was complete resolution. The estimated rate for this is 11 per million doses for the Pfizer product and 2.5 per million doses for the Moderna vaccine. In response to these findings, the US Centers for Disease Control and Prevention has issued guidance on prevention and management of this vaccine-associated anaphylaxis, including ensuring that vaccination sites have supplies and trained staff to manage anaphylaxis, that potential vaccine recipients are screened to identify persons with past anaphylaxis to vaccines, and that all persons have post-vaccination observation periods (Shimabukuro, MMWR).

Novel effects may also be seen with vaccine administration to persons outside of groups enrolled in clinical trials. A recent report has documented that the antibody response to the first dose of vaccine in persons with prior infection with SARS-CoV-2 may equal or exceed the response to a second dose persons without prior infection. As reactogenicity was also higher in those with prior infection, the possibility has been raised that these individuals may require only one dose of vaccine (Krammer).

Summary and Remaining Questions

Clinical trials and early observation from rollout show that vaccines do prevent severe illness and death and that incidence is decreasing with vaccine implementation. Questions remain, including vaccine use in children, efficacy against asymptomatic infection and viral shedding and viral variants, the durability of protection, and the need for booster doses to maintain immunity. Revaccination with products engineered to be effective against emerging variant strains also may be necessary. Fortunately, the pandemic is occurring in an era in which biotechnology has the potential to abort the global health crisis.

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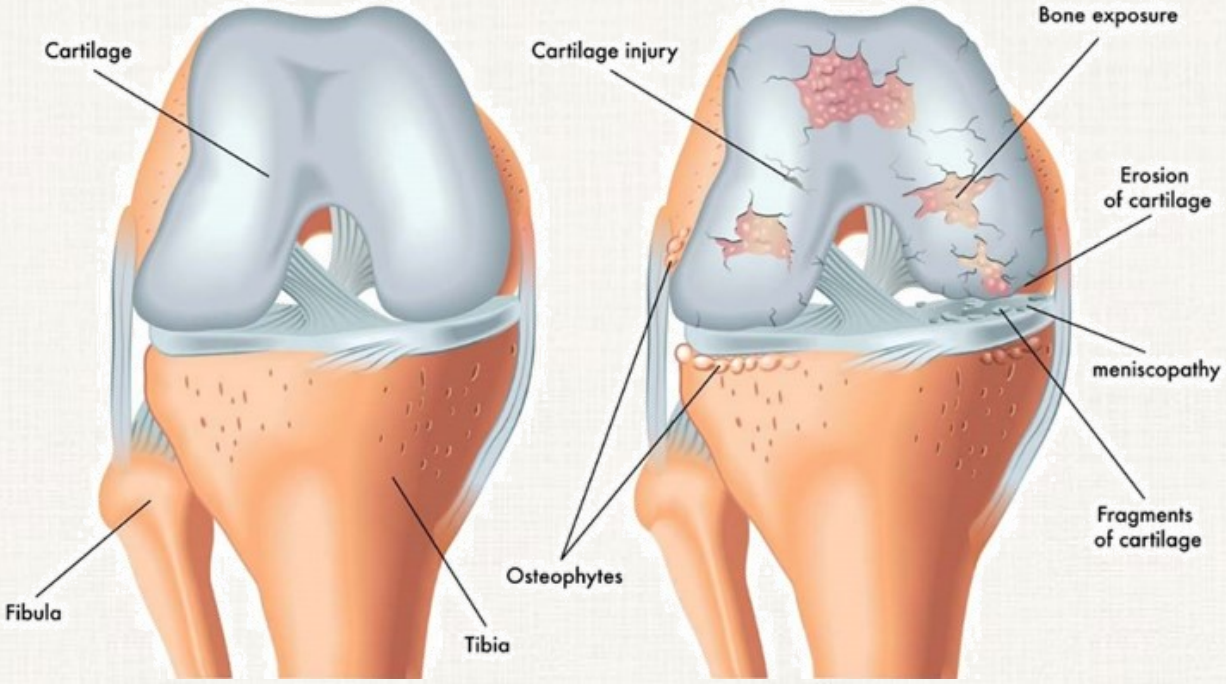
INA-RESPOND Newsletter

THE ROLE OF EXERCISE IN KNEE OSTEOARTHRITIS

By: Monica Surjanto



Knee Osteoarthritis2

Introduction

Osteoarthritis (OA) of the knee is the most common type of arthritis. The major cause of chronic musculoskeletal pain and mobility disability in the elderly can cause pain, fatigue, and functional limitations. While OA's prevalence increases with age, there is also growing evidence that OA affects people at younger ages.1

Knee OA is characterized by structural changes in and around the knee joint. The predominant structural changes are the loss of cartilage and the formation of osteophytes. These changes are easily demonstrated radiographically, and objective measures of disease severity are based on the amount of joint space loss (a reflection of cartilage loss) and the presence of osteophytes.1

The Risk Factors and Symptoms of Osteoarthritis

The cause of OA remains unknown, though there is clear evidence for the major risk factor, such as:3

- Age: The risk of developing OA increases as someone gets older because bones, muscles, and joints are aging.
- Joint injury: A break or tear can lead to OA after years.
- Overuse: Using the same joints over and over in a job or sport can result in OA.
- Obesity: Extra weight puts more stress on a joint, and fats cells promote inflammation.
- Weak muscles: Joints can get out of the right position when there's not enough support.
- Genes: People with family members who have OA are more likely to develop OA.
- Sex: Women are more likely to develop OA than men.

The symptoms tend to build over time rather than show up suddenly. They include:3

- Pain or aching in the joint during activity, after long activity, or at the end of the day.
- Joint stiffness usually occurs first thing in the morning or after resting.
- Limited range of motion that may go away after movement.
- Clicking or cracking sound when a joint bends.
- Swelling around a joint.
- Muscle weakness around the joint.
- Joint instability or buckling (knee gives out)

The Management of Osteoarthritis

The current management of OA includes both pharmacologic and non-pharmacologic modalities. The well-known pharmacological approach for symptomatic treatment comprises oral administration of paracetamol, NSAIDs, opioids, and intra-articular corticosteroid injections. In recent years, numerous studies have demonstrated the effectiveness of exercise and physical activity for non-pharmacologic modalities.1

The Role of Exercise In Knee Osteoarthritis

The role of exercise in knee OA is to minimize or slow the pathological process in the OA joint because exercise increases cartilage nutrition and remodeling, increases the synovial blood flow, decreases swelling, and improves muscle strength. Exercise also helps in reducing pain and improving range of motion and connective tissue elasticity. Evidence suggests that aerobic, strengthening, and flexibility exercise can decrease pain and improve muscular strength, functional ability, and psychological well-being.1

Aerobic exercise

Aerobic exercise with low joint stress (such as walking, swimming, cycling, aquatic exercise) has beneficial effects on pain, joint tenderness, functional status, and respiratory capacity for patients with OA. Frequency is 3 to 5 times per week, 150 minutes per week for moderate-intensity or 75 minutes per week for vigorous-intensity, or a combination of both.4

Strengthening exercise

Patients with knee OA tend to have reduced muscle strength due to reductions in physical activity and pain inhibition. Quadriceps strength deficits have been reported in 20%–70% of patients with knee OA. Any improvement in muscle strength or peak power of the lower extremities with decreased levels of particular pain may be important and is a strong predictor of functional ability.1

The initiation phase of strengthening exercise is twice a week and works up to three times a week. The initial resistance loads and the range of motion of the exercises can be tailored to the patient tolerance. The goal should be to encourage training at an intensity to induce an RPE of 13–15 ("somewhat hard" to "hard") with a minimum of 24 hours rest between sessions. Maintenance of strength gains and function over time can be achieved by performing leg exercises at an intensity that induces an RPE of 15–16. Variety in

Knee strengthening exercises6

the exercise program can be done with different leg exercises, performing unilateral versus bilateral exercise, or substituting free weight exercise such as squats with dumbbells, lunges, or step ups on to a stair or platform while holding light weights.5

Flexibility exercise

Arthritis can limit your flexibility. By doing stretching daily, you can keep your joints from getting stiff. Gently move your joints around as much as you can and stretch to the point of feeling tightness but not pain. Patients should be instructed to hold a static stretch for 10-30 seconds (30-60 seconds for older adults). Stretching includes the quadriceps, hamstring muscles, iliotibial band (ITB), and Achilles tendon.1

Other Types of Physical Activity

Aerobic exercise, strengthening exercise, and flexibility are at the heart of a program for those with osteoarthritis. There are also benefits from these other options, such as Yoga, Pilates, Tai-Chi, balance exercise, and take more steps. Take more steps by using a smartphone or activity tracker to measure your progress and stay motivated. Gradually build up to 7000-9000 steps per day.

Tips and Precautions Before Exercise

- Start slowly. Try to be active when pain levels and stiffness are lowest. Increase your activity time or speed by no more than 10 percent each week.
- If you have a flare-up, swelling, or increased pain and stiffness, do not stop all activity. Keep doing gentle joint movements while you recover. Then start back slightly below the level that caused the flare-up.
- Decrease stress on your joints by losing weight. Even a 5 percent weight loss will boost the positive effects of physical activity.
- You may experience some discomfort with activity, but that doesn't mean you're damaging your joints. If the pain is greater, 2 hours after training than before, go easier or shorter next time.
- Do a warm-up and cool down at an easy pace for 5 to 10 minutes to ease your joints in and out of the more vigorous exercise.

Conclusion

Knee osteoarthritis (OA) is a major public health concern worldwide and one of the foremost causes of chronic disability in older adults. Preventive care is dependent upon the identification of risk factors for the development of incident knee OA. The symptoms are often associated with significant functional impairment and signs and symptoms of inflammation, including pain, stiffness, and loss of mobility. Conservative treatment has documented the effectiveness of exercise in reducing pain and disability. Evidence suggests that aerobic, strengthening, and flexibility exercises decrease pain and improve muscular strength, functional ability, and psychological well-being.

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INA-RESPOND Newsletter

WHY IS CHANGING HEALTH-RELATED BEHAVIOR SO DIFFICULT? WHY IS CHANGING JUST SO... DIFFICULT?

By: Aly Diana

COMIC CORNER

Human behaviors, including tobacco and alcohol consumption, dietary behaviors, physical activity, and sexual practices, play a key role in many of the leading causes of death in developing and developed countries. Even small changes in such behaviors can have substantial effects on population health outcomes. Interventions have been targeted at behavioral risk factors (e.g., stop smoking, reducing sugar/fat intakes), encouraging protective behaviors (e.g., health screening, routine exercising); improving adaptation to chronic and acute illness (e.g., adherence to medical advice), and changing health professional behaviors to improve the quality and efficiency of services. However, some of the interventions seem not to work, and some show limited success.

We, as health professionals or as friends or as individuals: when we are trying to encourage a certain healthy behavior(s), I believe that we have ever experienced how hard it is to be successful. To help understand why we failed, experts have identified six common errors that have made the business of health-related behavior change much more difficult than it needs to be. Personally, I have no expertise to judge whether fixing these errors is the magic recipe. However, I am certain that this may prove to be an interesting point of view, that we can learn and explore more.

The six errors are:

(Note: I just tried to summarise it while still used their words, but it is certainly better to read the full paper)

· It's just common sense

All too often, thinking about behavior change has been driven by the belief that human behavior is so obvious that it needs little or no serious thought. It leads to thoughts such as: "It is obvious what needs to be done, so let us just get on and do it." However, if changing behavior were simply about making

common sense, simple changes, and good choices, then we would all be able to make whatever changes we wanted whenever we wanted. Obviously, we do not. This kind of thinking ignores that human behavior is influenced by social and cultural factors and is the result of the complex interplay between habit, automatic reactions, and conscious choice.

· It is about getting the message across

Some argue that changing health behavior is simply a matter of getting the messages right. If we could only get the message out there in some form that people could understand and identify with, they would change in response.

However, this is a simplistic approach that does not consider the complex interplay of activities, decisions, and environmental factors that influence human behavior. Although it may work for some, it may not work with others.

· Knowledge and information drive behavior

All too often, we believe information from expert sources will drive behavior change. This stems from a belief in the traditional medical model of the doctor-patient relationship, which is based on the premise that the patient comes to the doctor for their expert knowledge and understanding. Giving people information does not make them change, although it is necessary to prepare people to change.

· People act rationally

Similarly, we're driven by a belief that people act rationally, meaning they will do what they know to be sensible and logical. If we tell people what is good for them and what they need to do to protect their health, they will do it. Again, however, they clearly do not. Smoking, eating, drinking, and the amount of physical activity people do are ingrained in their everyday lives, routines, and habits. These things help to define someone's identity. The idea that simply providing people with information will lead to them changing their sense of who and what they are (and prompt them to seek to be a different person from the one they are now) is false.

· People act irrationally

People can't be counted on to act rationally, but they do not act irrationally all of the time too. People have their own reasons for doing things; behaviors that persist tend to be functional for people. For example, women who live in very difficult circumstances with tightly constrained resources still find the money for cigarettes. When they are asked why, they say that sitting down for a smoke is the one opportunity in the day that they get a chance to do something completely indulgent for themselves. In their context, smoking is therefore not an irrational thing to do. It is arrogant to assume that people consume alcohol, chocolate, or cream cakes because they are irrational or are simply behaving thoughtlessly or stupidly.

It is important not to dismiss the explanations people give for what they do just because the medical evidence dictates that what they do carries a health risk.

· It is possible to predict accurately

Lastly, although we have made great strides in identifying key factors which shape behavior, it is still very difficult to say with any certainty how individual people will behave in any given situation. In even the most careful of our models, there is a great deal of difference in individual behavioral outcomes.

I will let the theories hanging there; hopefully, we can spend some time thinking about the way forward with these errors in mind. What will I do differently to make behavior change less difficult?

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