INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

December 2020

Sport & Lifestyle
Get Active, Every Move Counts!

New Year's Resolution:
Let's start with a positive attitude

SARS-CoV-2 Infection in Children: Characteristics and Theories of COVID-19 Infection and Transmission Dynamics

Science Corner

Antibody-Mediated Severe Disease in COVID-19: Plausible Mechanism and Concerns in SARS-CoV-2 Vaccine Development

NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2020


2021
HAPPY NEW YEAR

INA-RESPOND newsletter

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FEATURES

INA-RESPOND

Newsletter

TRIPOD & PROACTIVE Study Updates

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

STUDY UPDATES

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PARTICIPANT STATUS

Per 08 Dec 2020, the total ongoing TRIPOD study participants are 16 out of 490 enrolled participants. From those 16 ongoing participants, one is still on TB treatment while 15 are waiting for their 6-month post-treatment visit. Two hundred and thirty-eight participants have completed the study, while 234 participants are terminated early (including death). Therefore, there are still 3.3 % of participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, all participant from site 520, 570, and 590 have been completed the study. At the same time, 1 participant from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar), 10 participants from site 560 (RSUP dr. Kariadi Semarang), 4 participants from site 580 (RSUP dr. Sardjito Jogjakarta), and 1 participant from site 600 (RSUP dr. Adam Malik Medan) still need to be followed up.

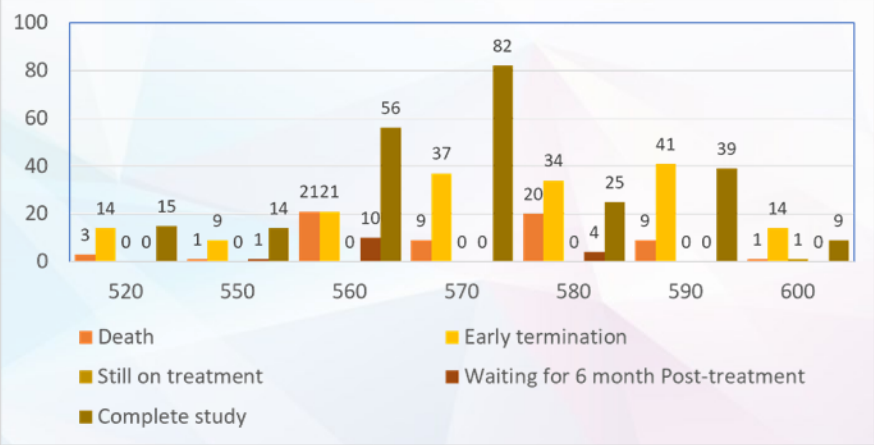


Figure 1. Participant status per site based on uploaded CRF per 8 December 2020

AWAITING CULTURE AND DST RESULT

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

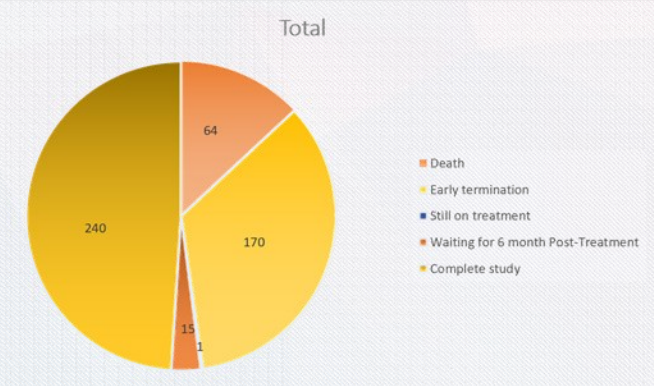


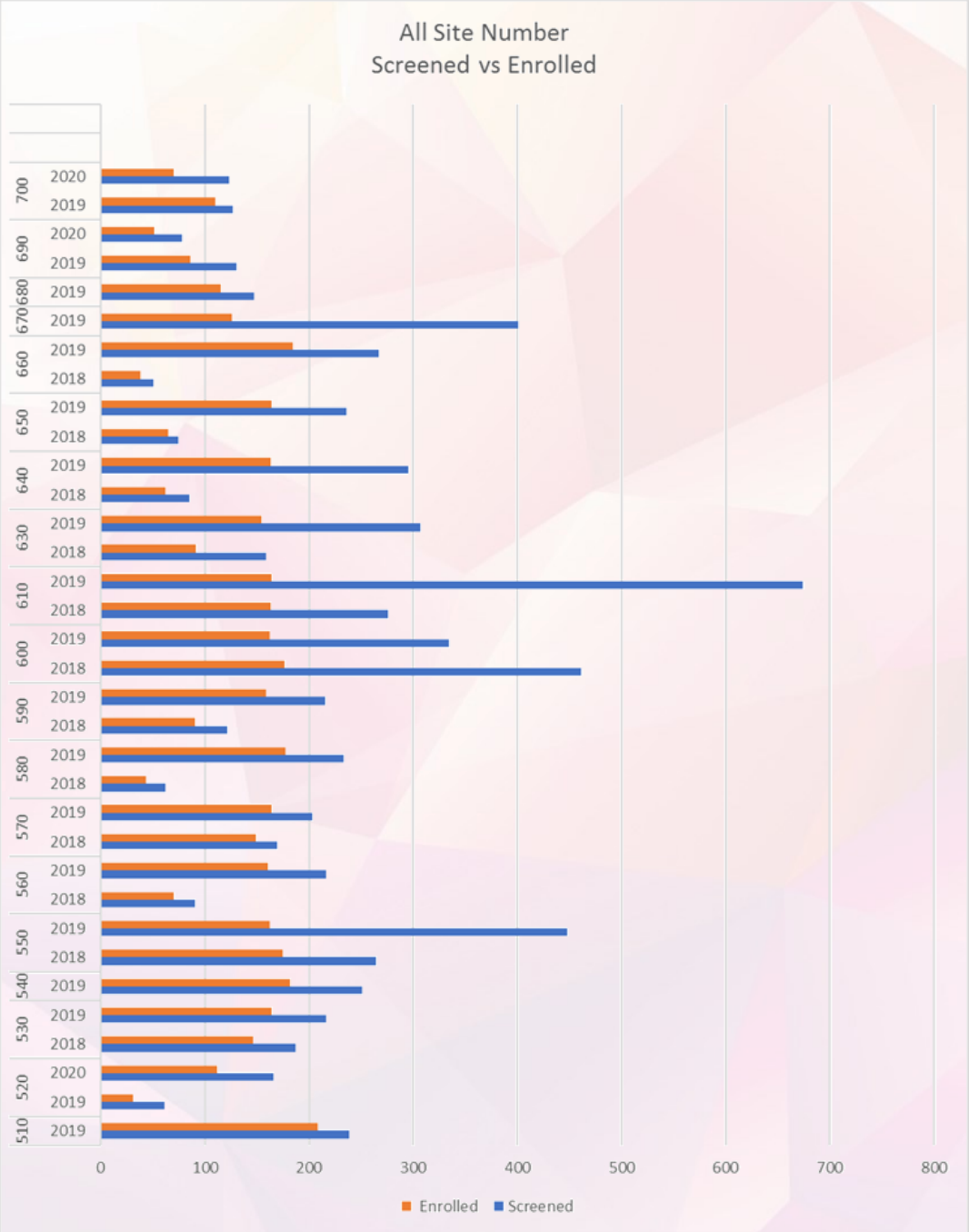
Figure 2. Total participant status based on uploaded CRF per 9 Nov 2020

Site	Waiting for Baseline Study Culture Result	Waiting for Baseline DST Result
520 (n=32)	Complete	Complete
550 (n=25)	Complete	Complete
560 (n=108)	Complete	Complete
570 (n=128)	Complete	Complete
580 (n=83)	Complete	Complete
590 (n=89)	Complete	Complete
600 (n=25)	Complete	Complete

INA104

INA-PROACTIVE study has entered its 2.5 years since the first activated site. Some of the INA-PROACTIVE sites have conducted the 30-month follow-up visit of their subjects. They are site 530 – Dr. Cipto Mangunkusumo Hospital, 550 – Dr. Wahidin Sudirohusodo Hospital, 570 – Dr. Soetomo Hospital, 600 – H Adam Malik Hospital, 610 – Tangerang Hospital, and 650 – Budi Kemuliaan Hospital.

The screening and enrollment of all 19 INA-PROACTIVE sites ended on 30 Jun 2020. As of 30 Jun, 4,336 subjects were enrolled, which consisted of 4,148 adults and 188 pediatrics from 7,364 subjects screened. Details are shown in figure 1. below:



All Site Number Screened vs Enrolled

As of 30 Dec 2020, 184 participants ended the study because of various reasons such as death or moving to another city with no site or far from INA-PROACTIVE study site hospital. Therefore, there are 4.152 active participants of INA-PROACTIVE to date.

In December 2020, one Site Monitoring visit (SMV) was done remotely on 2-3 Dec 2020 for site 700 – TC Hillers Hospital, NTT as the 2nd SMV.

INA-RESPOND Newsletter

ANTIBODY-MEDIATED SEVERE DISEASE IN COVID-19: PLAUSIBLE MECHANISM AND CONCERNS IN SARS-COV-2 VACCINE DEVELOPMENT

By: Wahyu Nawang Wulan & Ungke Anton Jaya

INTRODUCTION

As of December 11, 2020, SARS-CoV-2 infection has caused 71.4 million Covid-19 cases all over the world, 1.6 million of which are fatal. This has put a huge burden on the 218 countries affected; all of which are now counting on the availability of a safe and effective vaccine to end the pandemic. Massive global efforts to find the SARS CoV-2 vaccine is currently taking place, exploring candidates such as inactivated SARS-CoV-2 (e.g., CoronaVac by Sinovac Biotech), nucleic acid (mRNA) vaccines (e.g.,., mRNA BNT162b2 by Pfizer/BioNTech, mRNA1273 by Moderna), non-replicating vectored vaccines (e.g.,., AZD1222/ChAdOx1 nCoV-19 by The University of Oxford/AstraZeneca), as well as subunit vaccines (e.g.,., SCB-2019 by Sanofi Pasteur/GSK) [4].

As efforts are maximized to ensure immunogenicity, safety concerns emerge with regards to potential antibody-dependent enhancement (ADE) or other antibody-mediated severe clinical manifestation that is unexpected from vaccination. The presence of a specific antibody can create a condition that enhances the severity of the disease instead of allowing virus clearance, as has been well described in infection by dengue virus (DENV) and respiratory syncytial virus (RSV). There is an indication of antibody-facilitated severe outcomes in SARS-CoV infection, whereas SARS-CoV is the closest human Coronavirus (hCoV) to SARS-CoV -2 with 79.6% genomic sequence homology. As such, consideration on potential severe outcomes of SARS-CoV-2 infection associated with vaccine-elicited antibodies is reasonable. In this article, we review available evidence to identify potential risks of antibody-mediated severe disease in SARS-CoV-2 infection.

Antibody protection against viral infection occurs by neutralization or effector functions. Antibody-facilitated neutralization blocks viral entry or fusion, whereas antibody-facilitated effector recruits the components of immune response that consist of complement, phagocytes, and natural killer (NK) cells, to clear the infection [3]. Proving antibody-mediated severe disease requires careful analysis because the mechanisms used in antibody -mediated protection and antibody-mediated detrimental outcomes both occur through the similar processes of neutralization or effector functions. However, in a certain condition, including sub-neutralizing or cross-reactive but non-neutralizing antibodies, do antibodies switch roles to trigger harmful immunopathology.

No biomarkers can now distinguish between antibody-mediated or non-antibody-mediated severe disease. Massive efforts in in vitro (cell culture) and in vivo (animal model) experiments, as well as clinical or epidemiological observation, are required to uncover the mechanisms of antibody-mediated severe infection. Currently, the mechanisms are well understood in Dengue virus (DENV) and respiratory syncytial virus (RSV) infection.

ANTIBODY-DEPENDENT ENHANCEMENT (ADE) IN DENGUE VIRUS (DENV) INFECTION

Infection by DENV can manifest as mild dengue fever (DF) or the life-threatening dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). DENV exists as four different serotypes, known as dengue virus serotypes 1, 2, 3, and 4 (DENV-1,-2,-3,-4). Pre-existing serotype-specific antibodies neutralize subsequent infection by similar DENV serotype (homologous, protective) but are non-neutralizing for subsequent infection by different DENV serotypes (heterologous, not protective). The ADE concept of DENV infection proposes that heterotypic non-neutralizing antibodies or waning concentration of homotypic antibodies form a virus-antibody complex that facilitates entry using the FcγR via phagocytic pathway (Figure 1A) into monocytes, macrophages, or dendritic cells. FcγR-upregulated intake of antibody-opsonized DENV provokes modulation of innate immune effectors to favor more proliferation and strong inflammatory responses (Figure 1B) that cause enhanced severity of the disease [8, 9].

MECHANISM OF ANTIBODY-MEDIATED SEVERE RESPIRATORY SYNCYTIAL VIRUS (RSV) INFECTION

An antibody-mediated detrimental effect causing severe bronchiolitis and pneumonia was observed in rhesus macaques vaccinated with formalin-inactivated RSV (FI-RSV) and challenged with RSV A2 [10]. Vaccine-elicited non-neutralizing antibodies form antibody-antigen immune complexes (ICs) with incoming virus, which subsequently activate complements and trigger Th2 immune response [11] that provokes airway hyperresponsiveness (bronchoconstriction) [12] [13]. This mechanism is known as

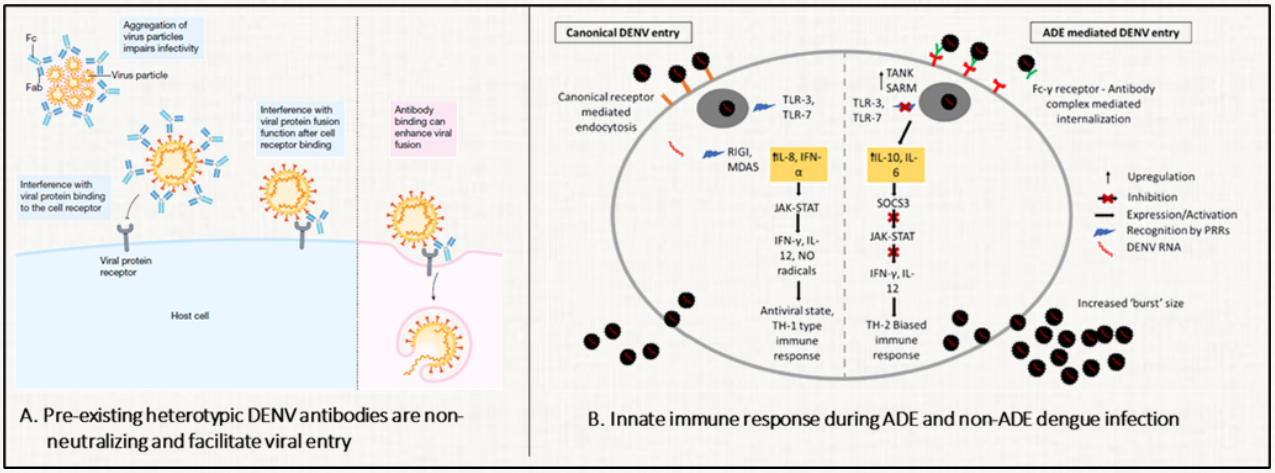


Figure 1 The ADE concept in DENV infection.

A. *Pre-existing heterotypic DENV antibodies are non-neutralizing and facilitate viral entry. Pre-existing heterotypic DENV antibodies complexes with infecting DENV and attaches to Fcγ receptors (FcγR) expressed on the surface of monocytes, macrophages, or dendritic cells to enhance cell entry via phagocytic pathway, instead of the clearing endocytic pathway. Image courtesy of Arvin et al., 2020 [3].*

B. ***Innate immune response during ADE and non-ADE dengue*** *infection. In canonical non-ADE, virus entry occurs via receptor-mediated endocytosis, where the DENV is internalized in endosomes and recognized by the pathogen recognition receptors (PRRs) Toll-like receptors (TLR-3) and 7. Release of viral RNA from endosomes is recognized by the retinoic-acid inducible gene 1 (RIG-1) and melanoma differentiation associated gene 5 (MDA5) which triggers production of pro-inflammatory cytokines IFN-α and IL-8. This activates the JAK/STAT pathway to cause expression of IFN-γ, IL-12, and nitric oxide (NO) that activates T-helper type 1 (Th1) responses, which limits DENV replication and spread. In ADE, DENV entry happens via antibody-FcγR binding. This complex inhibits TLR expression and signalling instead, and promotes the expression of negative regulators of TLRs, i.e the TAF family associated NF-kB activator (TANK) and sterile-alpha and armadillo motif containing protein (SARM). Inhibition of TLR signalling prevents the activation of JAK/STAT pathway and causes a T-helper type 2 (Th2) biased immune response allowing burst replication of virus particles. Image courtesy of Tripathi & Narayan, 2020 [6].*

vaccine-associated enhanced respiratory disease (VA-ERD) (Figure 2) [2], which caused deadly severe pneumonia in infant vaccinees during the clinical trial of FI-RSV vaccine in the late 1960s. It was later described that live RSV and FI-RSV have a different conformational state in the surface F protein that might impact their immunogenicity; where live RSV have pre- and post-fusion conformation while FI-RSV only have the post-fusion conformation, and only the pre-fusion conformation is thought to induce expression of the protective neutralizing antibodies [14].

An important lesson of antibody-mediated severe infection is that pre-existing non-neutralizing antibodies, elicited naturally, such as the case of DENV, or artificially, such as the case of RSV, can trigger harmful immunopathology through various mechanisms, including ADE or ERD. This condition has halted the development of tetravalent dengue vaccine to elicit neutralizing antibodies against four DENV serotypes at the same time.

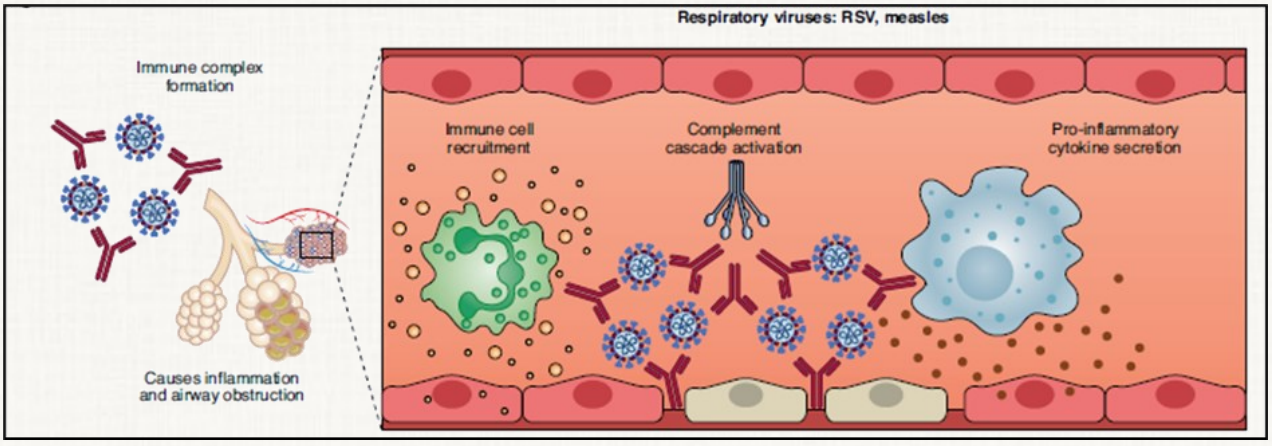


Figure 2 Antibody-mediated ERD

In non-macrophage-tropic respiratory viruses, pre-existing non-neutralizing antibodies form ICs with subsequently infecting virus, causing the secretion of pro-inflammatory cytokines, immune cell recruitment and activation of the complement cascade within the lung tissue. The ensuing inflammation leads to bronchiolitis/airway obstruction that causes acute respiratory distress syndrome (ARDS) in severe cases. Image courtesy of Lee et al., 2016 [2].

Following serious consequences of antibody-mediated severe manifestation in DENV and RSV infection, exploration has been done in other viruses where some promising evidence was generated. For example, influenza A virus propagated in primary mouse macrophages replicated more in the presence of anti-hemagglutinin IgG mAb [15] whereas Ebola Zaire virus infectivity in green monkey kidney cell line (Vero E6) increased in favor of sub neutralizing titre of human serum from a patient previously infected with Ebola Zaire strain Mayinga [16]. Observation of antibody-mediated exacerbation of infection in those viruses indicates potential adverse effects from pre-existing non-neutralizing antibodies in many varieties of viruses.

With regards to SARS-CoV-2 vaccine development, the probabilities of antibody-mediated detrimental effects of the vaccine are also considered. No evidence of antibody-mediated severe infection in SARS-CoV-2 infection is reported. Some insights could possibly be inferred from experiences with its closest relative, the SARS-CoV. The SARS-CoV that emerged in 2002 is the most homologous endemic hCoVs to SARS-CoV-2 (79.6% genomic sequence identity) compared to NL63 and 229E (Alphacoronaviruses) as well as OC43 and HKU1 (Betacoronaviruses) [17].

ANTIBODY-MEDIATED SEVERE INFECTION IN SARS-CoV

Severe respiratory disease associated with pre-existing antibodies against endemic hCoVs occurred during the SARS-CoV outbreak in the early-2000s in Taiwan. Ho et al., (2005) reported that severity was significantly higher (mortality rate = 29.6%) among some early seroconverters, i.e. patients who became seropositive within 2 weeks, in comparison with those who seroconverted after 3 weeks (mortality rate = 7.8%) [18]. The level of anti-SARS-CoV IgG were later shown to be higher among those with high degree of severity, i.e. required O2 therapy, than those who did not [19]. This severe manifestation on those with a faster and higher titre of IgG expression is associated with the priming effect of a previous infection with other endemic hCoVs, since after it was found that antibody against SARS-CoV cross reacts with antibodies against hCoV 229E and OC43 [20].

The mechanism of the antibody-mediated severe infection was then studied in in vitro (cell culture) and in vivo (animal model) experiments. Increased entry of replication-competent SARS CoV particles via FcγR occurred in primary human macrophages in the presence of anti-Spike (S) protein antibody [21], although the infection did not result in productive viral replication and shedding. In fact, the antigen-specific antibody that facilitates the intake of SARS-CoV particles via FcγR is not a distinguished event since it is a phagocytic route commonly used in virus clearance, such as in influenza A [22]. In an in vivo experiment, the FcγRIIa (CD32) – assisted SARS-CoV intake [21] was shown to cause tissue damage in rhesus macaque lungs that were vaccinated with formalin-inactivated SARS-CoV [23].

In short, S protein-mediated SARS-CoV entry into human macrophages is augmented by the binding between pre-existing anti-S antibody and the FcγRIIa cellular receptor and the resulting infection is detrimental, although abortive. The binding of SARS-CoV S protein and anti-S antibody was later shown to happen at the major immunodominant S597-625 motif (597LYQDVNC603TDVSTAIHADQLTPAWRIYSTG625), in which L597, Y598, Q599, D600, and/or C603 are critical residues in the enhancement of infection [23]. These amino acid residues lie close to the C-terminus of the SARS-CoV major receptor (ACE2) – binding domain (RBD) [24].

As SARS-CoV infection in macrophage is unproductive, disease exacerbation via elevated particle intake into macrophages, or ADE, is therefore not plausible. Should antibody-mediated disease worsening take place in SARS-CoV infection, the more plausible pathway is via formation of ICs inside airway tissues that promotes the secretion of pro-inflammatory cytokines, immune cell recruitment, and activation of the complement cascade within the lung tissue, leading to ERD [2](Figure 2), of which the mechanism has not been identified.

POTENTIAL ANTIBODY-MEDIATED DETRIMENTAL EFFECTS IN SARS-COV-2 VACCINATION

Due to the emergency nature of the COVID-19 pandemic, the race for a vaccine candidate has taken on exceptional urgency and commitment at the global level. Established organizations, government bodies, biotechnologies industries, pharmaceutical companies, as well as various initiatives including the WHO, GAVI, CDC, FDA, etc. are involved in an unparalleled data sharing and collaborative international strategy for a coordinated vaccine development to shorten the traditional pipeline of approved vaccine from the usual >10 years down to 12–18 months.

The lengthy process of vaccine development is done to ensure the safety and efficacy of the vaccine, which involves design stage, pre-clinical and toxicity tests, clinical trials: phase I (<100 individuals), phase II (few hundred individuals), phase III (thousands of individuals), license application, mass production, and post-marketing tests. Some phases can last up to 2 years or more, but these are now accelerated such that vaccine candidates from big pharma, including BNT162b2 (Pfizer/BioNTech) and mRNA1273 (Moderna) already passed the safety and efficacy requirement by the first interim of phase III of clinical trial in November 2020.

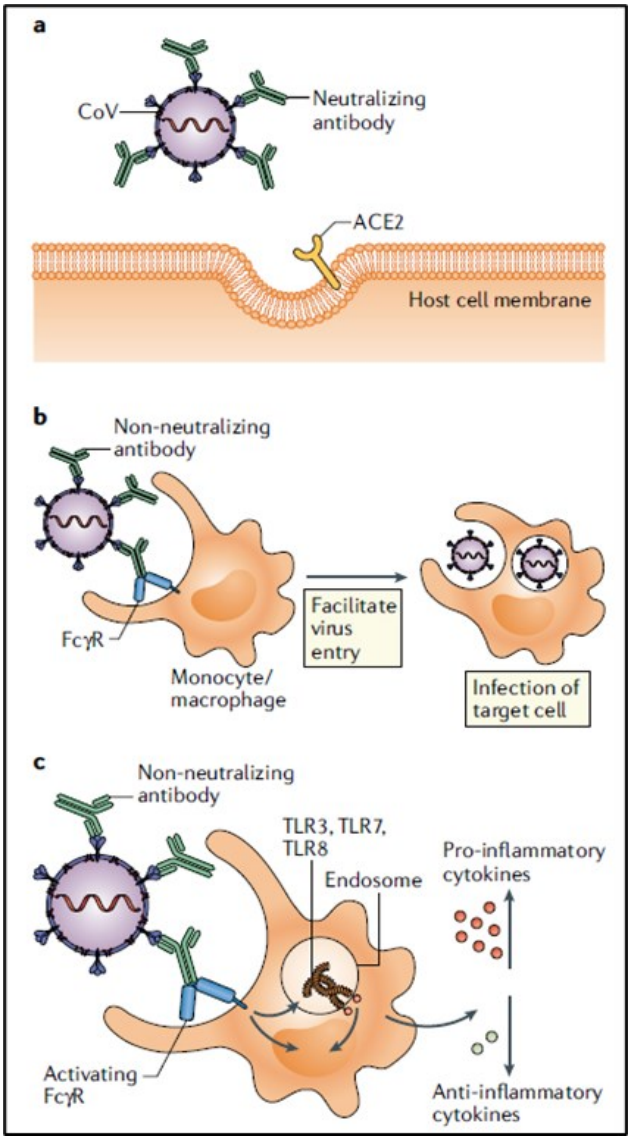


Figure 3 Possible outcome of vaccine-elicited *antibodies of SARS CoV-2:* ***a.*** *neutralization,* ***b.*** *antibody-dependent enhancement (ADE),* ***c.*** *enhanced respiratory disease (ERD). Image courtesy of Iwasaki & Yang, 2020 [1]*

To give protection against Covid-19 infection, the vaccine must be able to provoke a robust immune response that generates neutralizing antibodies against SARS-CoV-2 (anti S protein) while limiting potential serious adverse events (SAEs). In general, based on theoretical knowledge [19-21, 23, 25], possibilities of vaccine-elicited SARS CoV-2 antibodies in response to the incoming SARS CoV-2 infection are:

Neutralization. The vaccine – elicited antibody neutralizes SARS-CoV-2 particles and prevents the binding of RBD in S protein to ACE2 (Fig 3-a).

ADE. The vaccine–elicited antibody does not neutralize the SARS-CoV-2 but binds to FcγR on the surface of macrophages to assist particle entry (Fig 3-b). Evidence in in vitro and in vivo infection of SARS-CoV present that macrophage infection is detrimental but unproductive, although organ damage is possible.

VA – ERD. The vaccine – elicited antibody does not neutralize SARS-CoV-2 and instead forms immune complexes (ICs) with the viral particles (Fig 3-c). ICs can initiate signalling that upregulate pro-inflammatory cytokines and cause airway hyperresponsiveness, manifested as severe respiratory infection.

SARS-CoV-2 infection is initiated by the binding of viral spike (S) protein to the cellular entry receptor, angiotensin-converting enzyme 2 (ACE2). ACE2 is expressed on alveolar type II pneumocytes, airway epithelial cells, nasal tract goblet cells and ciliated cells, as well as on intestinal and other non-respiratory tract cells [26]. Having cellular entry receptor dispersed mainly in epithelial lining cells of the airways, should antibody-mediated disease enhancement take place in SARS-CoV-2 infection, the most plausible pathway is thought to be the formation of immune complexes (ICs) mediated by non-neutralizing antibodies, causing airway hyperresponsiveness leading to ERD [2] (Figure 2 / Figure 3c).

Concerns for antibody-mediated disease enhancement in SARS-CoV-2 appeared following a report of strong positive correlation between the high titer of anti-SARS-CoV-2 antibodies and critical COVID-19 condition (ARDS, oxygen saturation <93%, requiring mechanical ventilation) within 14 days after onset [27] as well as the observation of a higher and more persistent viral load in patients with severe disease outcome [28]. Pre-existing antibodies elicited by hCoVs (HKU1, OC43, NL63, 229E, SARS-CoV) could theoretically cause antibody-mediated disease enhancement via cross-reactive recognition of SARS-CoV-2 S protein without neutralizing the virus. Evidence presently exist for in vitro cross-reactivity and non-neutralization between antibodies against SARS-CoV and those against SARS-CoV-2 [29], whereas reactivity and neutralization with other hCoVs is not yet known. Since antibodies against SARS-CoV cross react with antibodies against 229E and OC43, possibilities of antibody-mediated severe disease in SARS-CoV-2 infection might exist as well.

A possible mechanism leading to the existence of cross-reactive non-neutralizing anti-SARS-CoV-2 antibodies is in response to antigenic sensitization of a different form of major determinant antigen, the spike (S) entry protein, taking a lesson from FI-RSV vaccination. FI-RSV has only the post-fusion form of F protein on the surface of virus particles, which although induce the expression of high-titre reactive antibodies, but are of low-neutralizing capacity and instead form ICs with incoming virus, causing disease exacerbation through activation of Th2-biased immune response [14]. The neutralizing anti-SARS-CoV-2 antibody against the spike (S) protein is specifically directed to disrupt the

interaction between RBD and ACE2 receptor [30]. The structure of SARS-CoV-2 S protein is a homotrimer built from the N-terminal S1 and the C-terminal S2 subunits, with S1 contains receptor-binding domain (RBD) that mediates host-cell receptor recognition and S2 plays a more important role during fusion (Figure 4A) [31]. The SARS-CoV-2 S protein also has different conformational states, where in pre-fusion state the trimer is in a wide clubhead-shaped, with receptor-accessible state having one or two RBDs rotated "up" and resting stage adopting all RBD "down" (Figure 4B) [5]; whereas in post-fusion state it is more a thin nail-shaped (Figure 4C) [7] and is thought to have only the S2 subunit, similar with the post-fusion structure of SARS-CoV S protein [32].

Different conformations of the major antigenic determinant S protein are important consideration in evaluating the neutralizing activity of anti-SARS-CoV-2 antibody. In human population, it is not yet known whether antibody against the pre-fusion form of SARS-CoV-2 S protein has a higher neutralizing activity than antibody against its post-fusion state. However, this consideration has been adopted as a precautionary measure in vaccine design, i.e stabilizing the pre-fusion state of SARS-CoV-2 S protein to minimize vaccine reactogenicity while enhancing the immunogenicity. One of the stabilizing efforts is by introducing two consecutive proline substitutions (S2P: K986P, V987P), with the reason that these residues are located in a turn between the heptad repeat 1 (HR1) and central helix (CH) of the S2 that function in the transition of the S2 subunit into a single, elongated α-helix in the post-fusion state [33]. Those substitutions prevent the structural transition, and have been applied in the design of NVX-CoV2373 (a recombinant SARS-CoV-2 nanoparticle vaccine composed of trimeric full-length S protein and Matrix-M1 adjuvant, Novavax/Emergent Biosolutions) and mRNA-1273 (mRNA encoding the stabilized prefusion SARS-CoV-2 S protein, ModernaTX Inc.) [34, 35].

To satisfy the safety of SARS-CoV-2 vaccine, evidence of antibody-mediated disease enhancement must be validly established from in vitro (cell culture) and in vivo (animal model) experiments, followed by clinical or epidemiological studies in human population [3]. In vitro experiments are required to explain the molecular mechanism of antibody-mediated disease exacerbation; most importantly to determine what epitopes used by the virus [23, 36]. Activation of immune response relies on the form of the viral protein that is recognized by the immune system, as either protective or non-protective antibodies can be elicited to

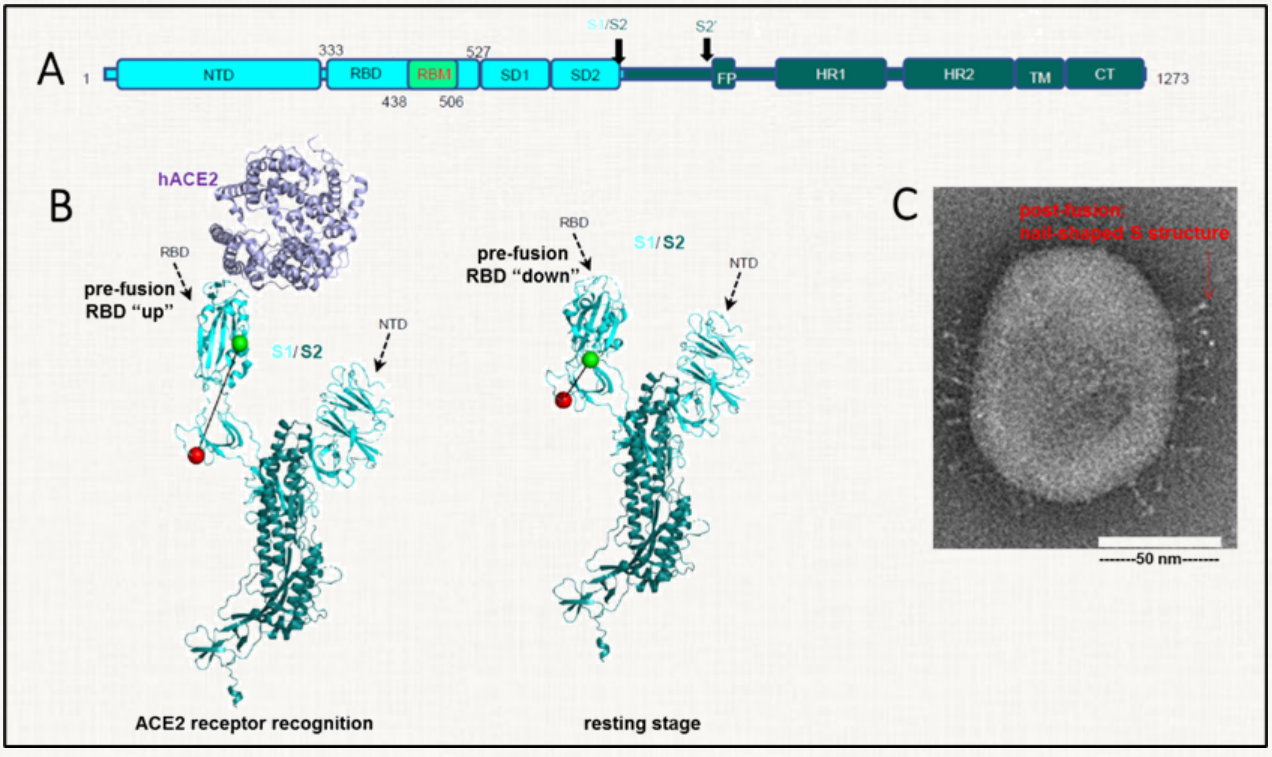


Figure 4 ***A. Domain organization of SARS-CoV-2 spike (S) protein*** *(1,273 amino acids). Receptor binding domain (RBD) is contained within the S1 structure. NTD: N-terminal domain, S1/S2, S2': protease cleavage sites, SD1: subunit domain 1, SD2: subunit domain 2, FP: fusion peptide, HR1/HR2: heptad repeat 1/heptad repeat 2, TM: transmembrane domain, CT: cytoplasmic tail.* ***B. Schematic of pre-fusion*** *conformation of the S protein. Pre-fusion structure is built from homotrimeric S1 and S2 subunits with RBD presented "up" during recognition of ACE2 receptor and presented "down" in resting stage.* ***C. Schematic of post-fusion conformation of the S*** *protein. Post-fusion form is built only from the S2 subunit and adopts a thin nail-like structure. Images courtesy of Lu et al., 2020 [5] and Liu et al, 2020 [7].*

different forms of the same protein [14]. Antibody-mediated exacerbation effect in vitro, however, does not necessarily represent or predict ADE/ERD without proof of the role of the antibody in the pathogenesis of a more severe clinical outcome, which need to be assessed in in vivo experiments. The evaluation in animal models should be judged cautiously because in general the effector functions of antibodies involve species-specific interactions between the antibody and cells of the immune system. In other words, antibodies can have very different properties in animals that are not predictive of those in human. The differences may inaccurately represent either the protective or immunopathological effects of antibodies, be they appear naturally or vaccine-induced. This leads to the need for clinical or epidemiological-based evidence in human population.

Vaccine strategies are directed toward adaptive immunity having memory against SARS-CoV-2, i.e by inducing the formation of neutralizing antibodies against the major antigenic determinant S protein, particularly those that can disrupt RBD-ACE2 interaction. Vaccine candidates are mostly entering the phase III clinical trials to assess their safety and efficacy, with two candidates have been granted the Emergency Use Authorization (EUA), the BNT162b2 (Pfizer/BioNTech; December 10, 2020) and mRNA1273 (ModernaTX, Inc.; December 18, 2020). With efforts are currently prioritized towards providing safe and effective vaccines, no reports on SARS-CoV-2 vaccine-mediated disease exacerbation have appeared. To understand what outcomes of SARS-CoV-2 vaccination might cause, post-vaccination studies need to be carefully established to acquire evidence on immune responses on SARS-CoV-2 infection in vaccinated individuals. Such studies might involve a prospective cohort to monitor antibody response on vaccinated individuals who get infected by SARS-CoV-2 in the future.

SUMMARY

Several evidence leading to potential antibody-mediated severity were observed during SARS-CoV infection during pre-clinical experiments. Still, the explanation on the mechanisms of the antibody in mediating disease severity has not been obtained. The 79.6% homology between SARS-CoV and SARS-CoV-2 genome generates concerns on potential antibody-dependent effect in SARS-CoV-2 vaccination. Incomplete evidence on cross-reactivity with antibodies against hCoVs does not help generate insights on whether pre-existing non-neutralizing antibodies from endemic hCoVs will trigger antibody-mediated severity among vaccinated individuals. Also, since SARS-CoV-2 is not a macrophage-tropic virus, the functional role of macrophage-tropic intake-assisting motif LYQDVNC (S597-603 in SARS-CoV / S611-617 in SARS-CoV-2) to mediate antibody-mediated disease enhancement phenomenon seems unlikely. A more plausible mechanism of the antibody's detrimental effect in SARS-CoV-2 infection is through vaccine-associated enhanced respiratory disease (VAERD), where the expression of non-neutralizing antibodies against S protein elicited by vaccine do not neutralize the virus and instead forms immune complexes (ICs) with the viral particles. Even so, more evidence generated by in vitro and in vivo experiments and epidemiological studies in the human population is urgently needed to confirm those possibilities.

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Non-standard Abbreviations and Acronyms

SARS-CoV-2	severe acute respiratory syndrome coronavirus 2 (a human coronavirus causing covid-19)
Covid-19	coronavirus disease 2019
hCoV	human coronavirus
SARS-CoV	severe acute respiratory syndrome coronavirus (a human coronavirus that emerged in 2002)
ADE	antibody-dependent enhancement
DENV	dengue virus
RSV	respiratory syncytial virus
DF.	dengue fever
DHF	dengue hemorrhagic fever
DSS	dengue shock syndrome
FcγR	Fc gamma receptor
NK.	natural killer
PRR	pathogen recognition receptor
TLR	Toll-like receptor
RIG	retinoic-acid inducible gene
MDA	melanoma differentiation associated
IFN	interferon
IL.	interleukin
JAK/STAT	Janus kinase-signal transducer and activator of transcription
NO	nitric oxide
Th	T helper
TANK	TAF family associated NF-κβ activator
SARM	sterile-alpha and armadillo motif containing protein
FIRSV	formalin-inactivated respiratory syncytial virus
IC.	immune complex
ERD	enhanced respiratory disease
IgG	immunoglobulin G
ACE2	angiotensin converting enzyme 2
RBD	receptor binding domain
SAE	serious adverse event
ARDS	acute respiratory distress syndrome
EUA	emergency use authorization

INA-RESPOND Newsletter

SARS-COV-2 INFECTION IN CHILDREN: CHARACTERISTICS AND THEORIES OF COVID-19 INFECTION AND TRANSMISSION DYNAMICS IN CHILDREN

By: Amelia Hayward

Introduction

The ongoing global COVID-19 pandemic represents the most significant challenge to public health since the 1918 influenza pandemic a century ago. As of December 22, 2020, there are just over 76 million confirmed cases globally and 1.7 million deaths (1). From its inception, clinicians have noted that the SARS-CoV-2 virus has caused varying degrees of severity of illness, ranging from asymptomatic cases to severe illness and death (2). However, despite its wide-ranging effects on the general population, one group seems to exhibit mostly mild cases of the disease: children.

Clinical Characteristics of SARS-CoV-2 Infection in Children

Children exhibit many of the same symptoms that adults do, with the most common symptoms reported being fever, cough, and shortness of breath (3, 4). Less common symptoms have included digestive issues (such as vomiting, nausea, and diarrhea), fatigue, muscle aches, and loss of taste and/or smell (5). When tracking the epidemiology of a fast-spreading, highly contagious, respiratory pathogen such as SARS-CoV-2, one of the first questions investigators ask is: What role do children play in the spread of this disease? Previous respiratory virus outbreaks have proven that schools can be a key link in the transmission chain (6). Health experts have been concerned that school-aged children and adolescents may be at significant risk for infection by SARS-CoV-2 (especially in school environments), particularly if community transmission is high. Children's role in spreading SARS-CoV-2 is still under investigation, as it remains unclear if schools can be origin points for super-spreader events. Current findings will be discussed in the next section. What is apparent, however, is that children overwhelmingly experience far milder cases and are at less risk for mortality than adults. In the early days of the pandemic in China, reports of pediatric cases of COVID-19 (the disease caused by SARS-CoV-2) were rare, but showed that more than 90% of the cases were asymptomatic, mild, or moderate (7). Similar results were reported in Italy, where the pandemic first took hold in Europe, with estimates that over 80% of cases in children were asymptomatic, mild, or moderate (3).

Global data regarding the true number of children who have contracted COVID-19 is lacking due to limited testing and the prioritization of testing symptomatic individuals. However, these trends persist and seem to suggest that children do not bear the same disease burden that adults do. Notable exceptions to this include infants less than 6 months old and children with certain underlying conditions. It should be noted that though data regarding COVID-19 infections in newborns are rare, there appears to be at a higher risk for developing severe illness. While newborns are born with maternal antibodies, these antibodies are not protective against SARS-CoV-2 infection (8). In addition, newborns have far smaller, less developed airways that put them at higher risk for respiratory infection. It also appears that the after the onset of puberty, the risk for being infected rises though it is still undetermined if this places

adolescents at higher risk for clinically severe cases of COVID compared to adults (9).

Similarly, children with underlying medical conditions (such as obesity, chronic kidney disease, asthma, and diabetes) are also at higher risk for severe illness than their counterparts without (10). Possibly the most concerning potential complication of COVID-19 in pediatric cases is multisystem inflammatory syndrome (MIS-C), a condition in which parts of the body become inflamed, such as the heart, blood vessels, kidneys, and skin. Experts are unsure what causes MIS-C, but evidence indicates that children who develop MIS-C test positive for COVID-19 antibodies (10).

Current Theories Regarding Mild Pediatric Cases

What factors might be able to explain children's less severe disease burden than adults? Though the scientific community continues to investigate, there are several theories. Children's immune systems are still developing, and thus, are unable to mount an adequate immune defense. The immune response is not strong enough to cause some of the more severe symptoms seen in the clinical course of adult cases (11). Another potential factor is that children's variety of memory T-cells to viruses has provided their immune systems with the ability to cross-react with the SARS-CoV-2 virus, possibly from previous infections with season human coronaviruses. Angiotensin-converting enzyme 2 (ACE2) receptor, the target of the spike protein on the SARS-CoV-2 virus, is not as highly expressed in the upper airways of children as it is in adults, which could contribute to less severe symptomology (6). Other potentially protective factors include lung infiltrates that arise as a result of respiratory infection (12).

As more studies are conducted with a focus on children infected with COVID-19, a clearer understanding of the transmission dynamics and characteristics of COVID-19 infection in children will come into view. Further areas of investigation will hopefully include the long-term effects of COVID-19 in children, as there is scientific precedent of viruses causing latent problems later. Children who were born asymptomatic for Zika virus were found to develop Zika-related problems later in life, including seizures and impairment of vision and brain development in their first year of life (13). The COVID-19 pandemic has posed unique challenges for the global community, much like the influenza pandemic of 1918. Though it is promising that children generally are spared from the potentially devastating effects of COVID-19, it is still paramount that they are monitored to mitigate the risk of spreading the disease.

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INA-RESPOND Newsletter

GET ACTIVE, EVERY MOVE COUNTS!

By: Marco Ariono

Recently, the World Health Organization (WHO) published new physical activity guidelines. WHO wants to reduce the global level of physical inactivity. The trend showed that one in four adults and more than 81% of adolescents don't meet the exercise recommendations.1

Figure 1 shows that early physical activity guidelines focused on continuous vigorous aerobic exercise, mainly for performance improvement or cardiac rehabilitation. The guidelines revised with much evidence on moderate-intensity physical activity benefits and evolved to become more public-health oriented.

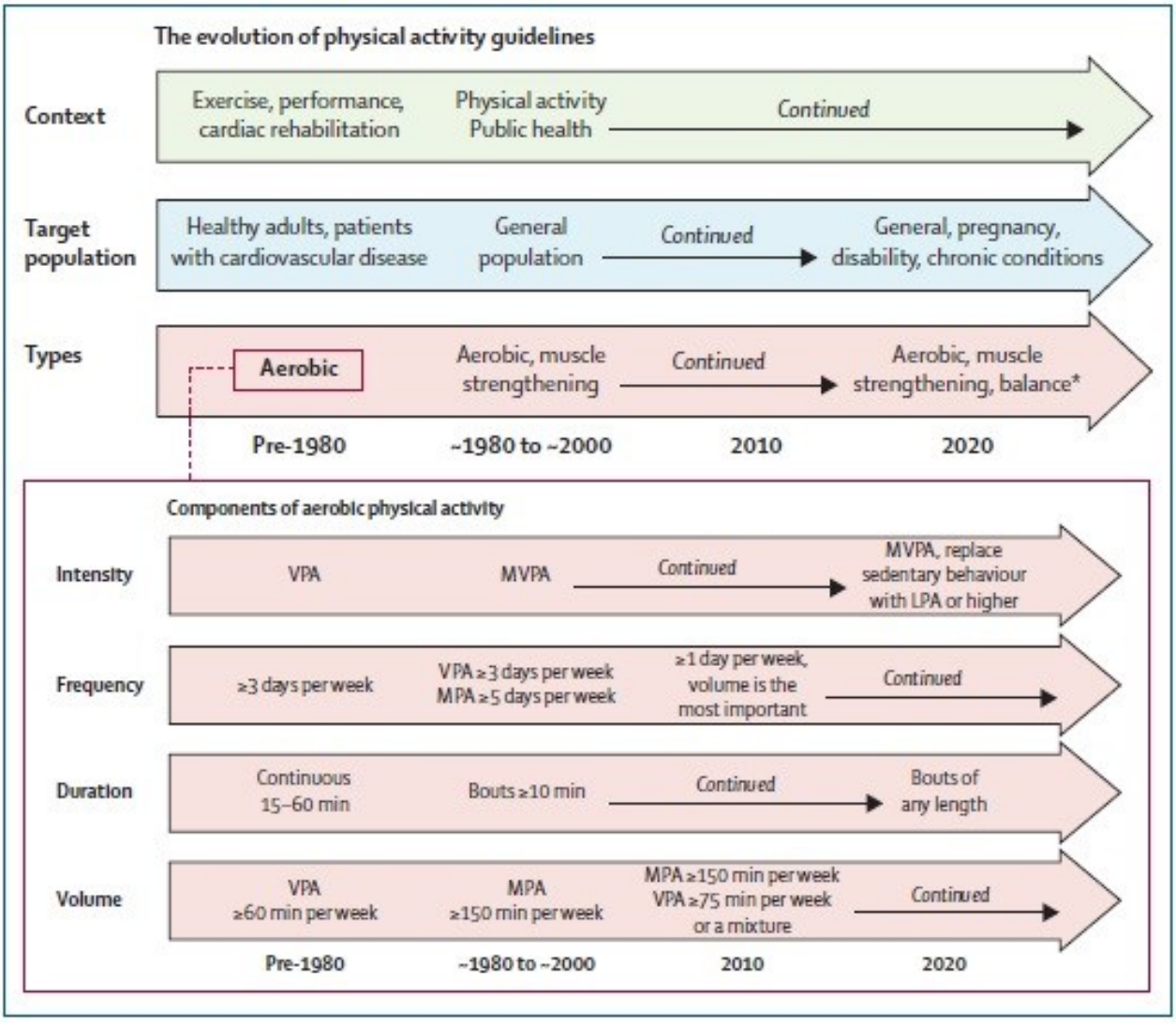

Figure 1. The evolution of physical activity guidelines and components of aerobic physical activity. VPA=vigorous-intensity physical activity. MVPA=moderate-to-vigorous intensity physical activity. MPA=moderate-intensity physical activity. LPA=light-intensity physical activity. *Primarily among older adults.2

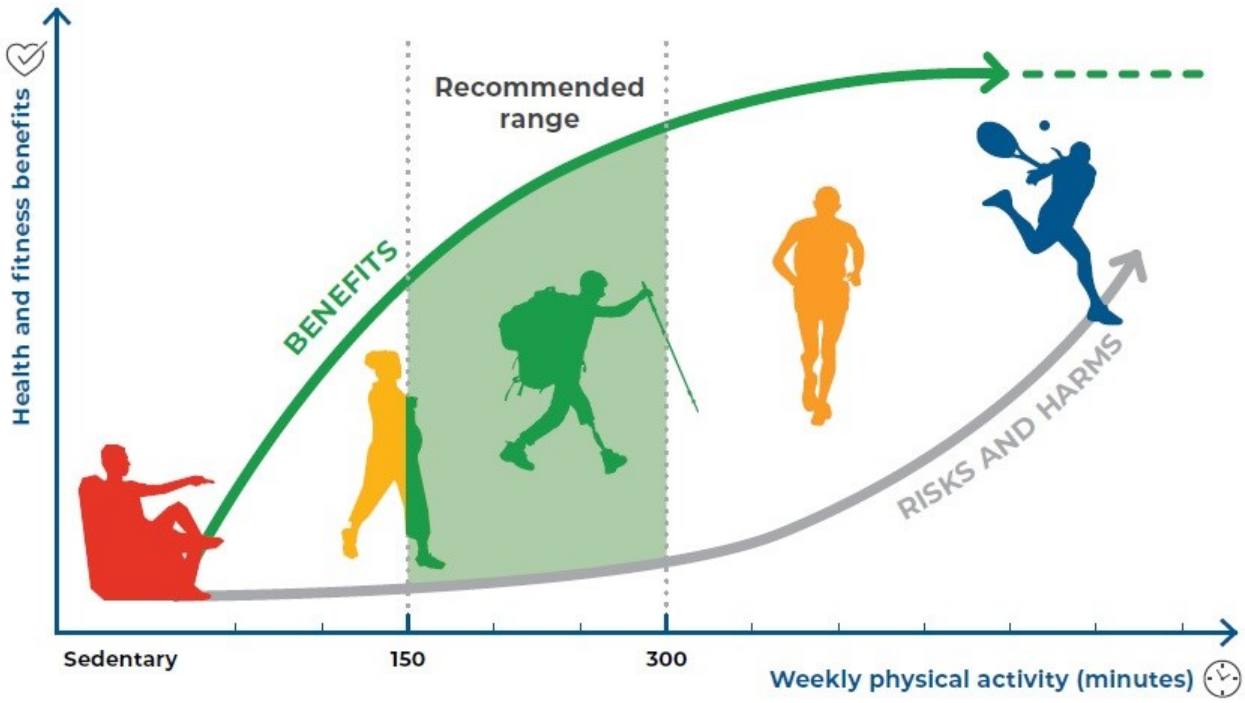

Figure 2. Dose-response curve7

The guidelines' focus shifted from exercise, which is planned and structured, to physical activity, which can be part of our daily activities.2

For all populations, doing some physical activity is better than doing none. Evidence suggests that light-intensity physical activity might benefit cardiometabolic health and reduce overall mortality risk. Always start with small amounts of physical activity and then gradually increase frequency, intensity, and duration. If someone wants to start exercise, usually medical clearance is unnecessary, especially if they don't have any contraindication. But if we develop new symptoms after exercise or after increasing exercise intensity, we should consult the doctor.1,3

Besides that, we should also limit our sedentary time. A meta-analysis by Ekelund et al. found that higher sedentary time is associated with higher mortality in less active individuals. Sedentary time more than 10 hours per day is associated with a higher risk of mortality. The risk increase for those who don't meet exercise recommendations.4

Recommendations for children and adolescents (5–17 years)

Higher screen time levels in children and adolescents are associated with health harms with the evidence strongest for adiposity, unhealthy diet, depressive symptoms, and quality of life. Higher screen time will contribute to higher sedentary time. Evidence suggests that physical activity has a positive effect on cognition and academic achievement.1,5

Physical activity in children will bring health benefits such as improved physical, mental, and cognitive. An average of 60 minutes of moderate to vigorous physical activity (MVPA) will bring many health benefits. Of course, we can add more duration for more than 60 minutes a day and get additional advantages. The new guidelines' notable update is the changing from 'at least' 60 minutes MVPA a day to 'an average' 60 MVPA per day.1

Recommendations for adults (18–64 years)

Evidence showed that all adults should do regular physical activity. Some activity is better than none. An adult should do aerobic exercise with moderate intensity for 150-300 minutes weekly or 75-150 minutes with vigorous intensity or an equivalent combination of MVPA. Besides that, adults also should do muscle-strengthening exercises at least twice a week. The difference with previous guidelines is 2010 WHO guidelines mention only specific minimum weekly thresholds. The new guidelines also remove the minimum 10 minutes bouts of exercise. Any duration of exercise showed health benefits. This guideline support statement that some physical activity is better than none.1,6

Recommendations for older adults (65 years and above)

Older adults should do multicomponent physical activity at moderate or greater intensity three or more days a week. Physical activity is important for older adults because it will add health benefits to prevent falls, enhance functional capacity, and reduce osteoporosis risk. Evidence indicates that the risk of fall-

related injury may be decreased with multicomponent physical activity (combinations of balance, strength, endurance, gait, and physical function training). Low levels of physical activity are associated with an increased risk of mortality and chronic health conditions in people over the age of 65.1,8

Recommendations for special populations

Pregnant and post-partum women should participate in physical activity because physical activity during pregnancy is associated with reduced gestational weight gain and reduces the risk of gestational diabetes mellitus.1,9

Physical activity is also safe for adults living with chronic conditions without contraindications. The benefits outweigh the risks. The evidence found that people with chronic conditions can sustain aerobic physical activity for more than three months as a form of treatment.1,10

For people living with a disability without contraindications, physical activity is considered safe and beneficial. People living with a disability may need to consult with their doctor to help determine the type and amount of activity relevant for them.1

What's new?

The previous statement, which stated physical activity should last at least 10 minutes, has been removed. Evidence showed that any bout duration is associated with improvement of health outcome. The guidelines for an adult now specify a target range of 150–300 min of moderate-intensity and 75–150min of vigorous-intensity physical activity, compared with the previous guidelines that focused on achieving at least 150 min moderate-intensity or 75 min of vigorous-intensity exercise per week. The recommendation for older adults regarding the multicomponent physical activity that emphasizes functional balance and strength training to enhance functional capacity and prevent falls now applies to all older adults rather than those with poor mobility.

There is also a change in recommendations for children and adolescents from 60 minutes a day of MVPA to an average of 60 minutes of MVPA daily.1,6

Conclusion

All populations should do physical activity and limit sedentary behavior for benefits that outweighed the potential harms. The risk of physical activity can be managed by increasing the amount and intensity of physical activity gradually. Some physical activity is better than none for those not currently meeting these recommendations.1,4

So start with small amounts of physical activity, because every move counts!

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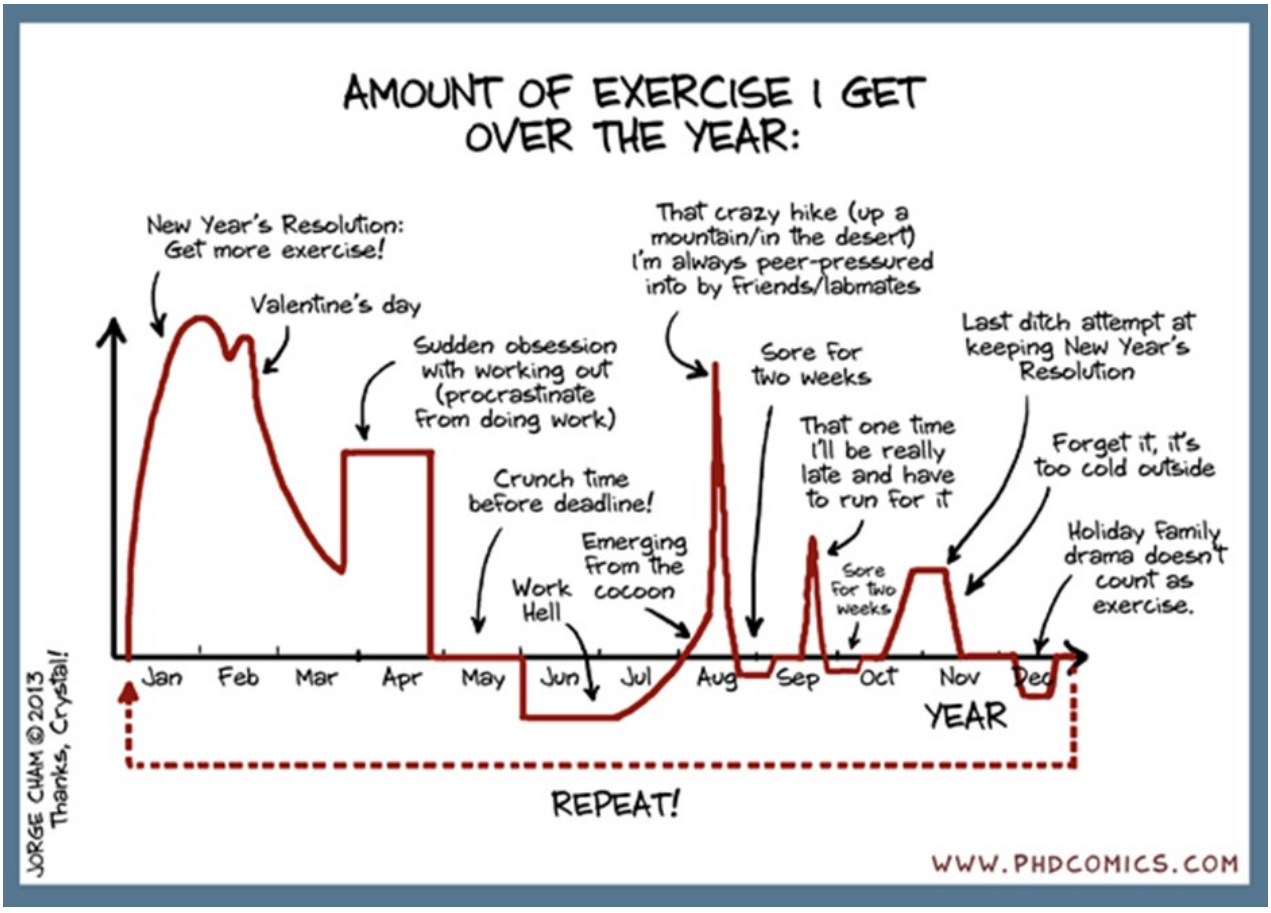
INA-RESPOND Newsletter

COMIC CORNER

NEW YEAR'S RESOLUTION: LET'S START WITH A POSITIVE ATTITUDE

By: Aly Diana



Source: "Piled Higher and Deeper" by Jorge Cham (www.phdcomics.com)

The year 2020 will always be remembered for most of us; I am sure that it was 'special' for one thing and many different reasons. Regardless of what happened last year, a new year is coming. New Year is a time when we make resolutions for doing better, finishing projects, stopping procrastination, and achieving goals. As expected and predicted, motivation is high on the first day of January, but it tends to decrease over time until the New Year's resolutions are ultimately abandoned. Surprise, surprise!

By making a resolution, people are setting goals that they want to pursue. People who had failed repeatedly to pursue their goals shared one of the most common reasons for giving up: it took too long/too many efforts before any results could be seen. Lack of self-confidence was also a common reason; some of us may start in a negative spiral, never believing that we would succeed, yet at the same time being desperately anxious to do anything to achieve our goals. With this attitude or mindset, frustration is common, while success is rare. So, first thing first, no matter what our goal is, let's

start with positive thinking and be resilient, as cliché as it may sound.

Next, more into the scientific approach, one line of research that fits with the process is goal-setting theory. The goal-setting theory examines how setting a goal influences subsequent performance in pursuit of that goal. Hundreds of studies show that challenging, specific, and concrete goals are powerful motivators and boost success in goal pursuit more than vague and abstract goals. For example, the specific goal (also called 'subordinate goal') "lose 10 pounds in 2 months" should be more successfully achieved than the vague goal (also called 'superordinate goal') "lose weight." From this perspective, the formulation of a New Year's resolution in the form of a subordinate goal should be a successful strategy.

However, in contrast to this relatively narrow focus, many of today's real-life goals hinge on broad, long-term goal-pursuit. For example, addressing a health problem such as overweight/obesity requires more than to "lose 10 pounds" once; it requires a continued healthy diet and regular exercise. After first achieving the subordinate goal, people must also continue to take goal-congruent actions, sustain motivation over the long term, resist the pull of competing goals and temptations, overcome compensation effects, and be resilient when faced with setbacks and failures. Subordinate goals alone may not be a "silver bullet" when addressing broad, long-term challenges. One approach that might help to improve the pursuit of New Year's resolutions over the year and to manage the transition between behavior initiation and maintenance is to incorporate a focus on superordinate goals into the plan. How important we perceive our goal is also an essential factor. For example, people who want to lose weight for improving health vs. improving appearance may become equally successful as long as they believe their goal is important for them.

Enough with theory, it's time for planning and following it with actions. Things to remember: set a goal(s) that can be achieved, do not suffer too much in the process, and do not curse yourself when you failed. Hope our New Year's Resolutions can be maintained longer this year. Happy New Year!

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