INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

October 2021

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Are Dengue Vaccines approaching the finish line?

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

MASTHEAD

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newsletter

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INA-RESPOND Newsletter

TRIPOD, PROACTIVE, & ORCHID Study Updates

By: Eka Windari R., I Wayan Adi Pranata, Lois E. Bang, Melinda Setiyaningrum, Nur Latifa Hanum, Retna Mustika Indah, Riza Danu Dewantara

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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. All study documents will be archiving at Indo Arsip and Final report for NIHRD will be submitted in the end of November. The status of document archiving is provided in figure 1.

Site	Site Closed Out Visit	Current Status/Awaiting Items
520 (n=32)	Done, 30 November – 1 December 2020	Study documents has been sent to Indo Arsip
550 (n=25)	Done, 22-23 June 2021	Site report has been finalized and signed by Head of Centre Two The notification letter for site close out and site report have sent both for the Central IRB (NIHRD IRB) and the Hospital Director The study documentation (SRB, SDW and Worksheet CRF) has sent to the INA-Respond Secretariat The INA-Respond Secretariat's team are working with specific packing the study documentation prior to Archive at Indo Arsip
560 (n=108)	Done, 20-21 April 2021	Study documents has been sent to Indo Arsip
570 (n=128)	Done, 15-16 December 2020	Study documents has been sent to Indo Arsip
580 (n=83)	Done, 14-15 September 2021	Site report has been finalized and signed by Head of Centre Two The notification letter for site close out and the site report have sent both for the Local IRB (Medical Faculty of UGM-IRB) and Central IRB (NIHRD IRB) The Hospital Director also has been notified in term of site close out for the study INA 102. The study documentation (SRB, SDW and Worksheet CRF) has sent to the INA-Respond Secretariat The INA-Respond Secretariat's team are working with specific packing for the study documentation prior to archive at Indo Arsip
590 (n=89)	Done, 19-20 January 2021	Study documents has been sent to Indo Arsip
600 (n=25)	Done, 21-22 July 2021	Site report has been finalized and signed by Head of Centre Two The notification letter for site close out and the site report have sent both for the Central IRB (NIHRD IRB) and the Hospital Director The study documentation (SRB, SDW and Worksheet CRF) has sent to the INA-Respond Secretariat The INA-Respond Secretariat's team are working with the specific packing for the study documentations prior to archive at Indo Arsip

Figure 1. Site Close Out Visit Schedule and updates Jun 2021

Other ongoing activities related to TRIPOD are; (1) Send the TRIPOD isolate to Central Laboratory in Padjajaran University Bandung on 12 April 2021 for subculture that will be prepared for several tests related to TB, including TB strain examinations which is one of the TRIPOD secondary objectives; (2) Collaboration within the Reports network on Epidemiology of TB Progression and Outcomes Study, using the TRIPOD data; (3) 1st Manuscript submission which is targeted to be done in early November; (4) Invite the network to submit the Ideas on TRIPOD specimens used. Per protocol, there are 8 types of specimens collected on TRIPOD study for future used. Status for Repository specimens is provided in figure 2.

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	20
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 2. Repository Specimens and Aliquots per May 2021

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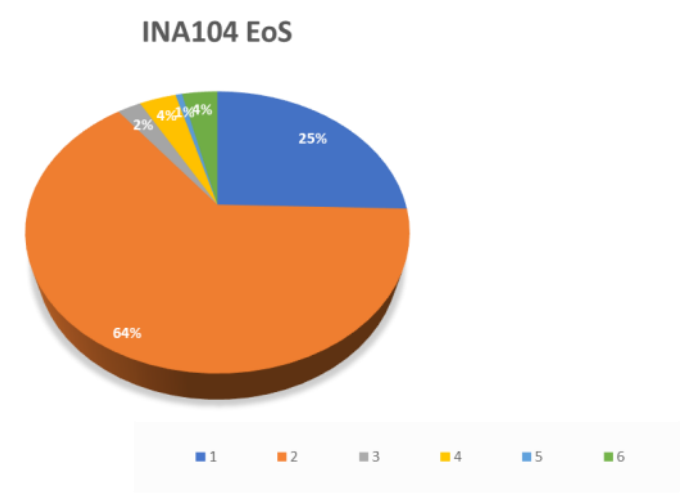
Study follow up are ongoing at all Sites. As of 1 Oct 2021, from 4,336 subject enrolled, 3,591 participants still active in the study, while 739 participants are end of study due to Death, move away, withdrew, and negative HIV. At the same time, 50 subjects were transfer between each Sites. Herewith the enrollment and active participant's detail:

No	Site# / Name	1st Enrollment	Enrollment stop	# Enrolled			Active Participants
				Ped	Adult	Total	
1	510 – Hasan Sadikin	07-Feb-19	31-Dec-19	10	198	208	201
2	520 – Sanglah	07-Nov-19	30-Jun-20	5	138	143	142
3	530 – Cipto M.	03-May-18	31-Aug-19	36	274	310	226
4	540 – Sulianti Saroso	25-Feb-19	31-Dec-19	20	162	182	176
5	550 – Wahidin	14-Mar-18	31-Aug-19	10	327	337	236
6	560 – Kariadi	14-Aug-18	31-Aug-19	12	218	230	196
7	570 – Soetomo	26-Apr-18	31-Aug-19	6	307	313	210
8	580 – Sardjito	14-Sep-18	30-Sep-19	4	216	220	215
9	590 – Persahabatan	19-Jul-18	31-Aug-19	10	239	249	217
10	600 – Adam Malik	12-Mar-18	31-Aug-19	2	336	338	239
11	610 – Tangerang	10-Jan-18	31-Aug-19	17	310	327	206
12	630 – Ansari Saleh	17-Jul-18	31-Aug-19	9	236	245	194
13	640 – St. Carolus	13-Aug-18	30-Sep-19	0	225	225	208
14	650 – Budi Kemuliaan	02-Aug-18	31-Aug-19	4	225	229	190
15	660 – AW Sjahranie	03-Oct-18	30-Sep-19	17	205	222	210
16	670 – Zainoel Abidin	09-Apr-19	31-Dec-19	5	121	126	119
17	680 – Soedarso	04-Jul-19	31-Dec-19	8	107	115	108
18	690 – Abepura	02-Jul-19	30-Jun-20	4	133	137	129
19	700 – TC Hilers	08-Jul-19	30-Jun-20	10	170	180	169
Total				**188**	**4,148**	**4,336**	**3591**

No	End Of Study Reasons	Total
1	Death	191
2	End of study duration (completed FU month 36)	481
3	Lost to Follow Up (did not complete FU month 36)	18
4	Participant who move away from the site where they are receiving HIV care and unable to comply with the study procedures	28
5	Participant with negative HIV test	5
6	Withdrew consent	27
Total		**750**



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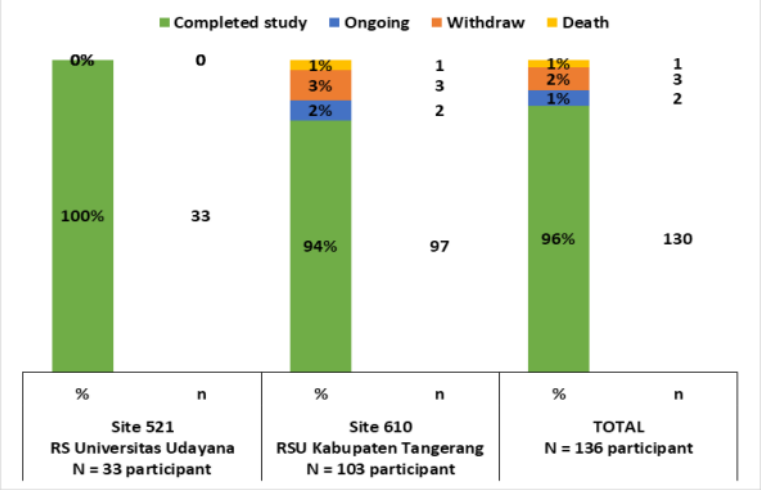
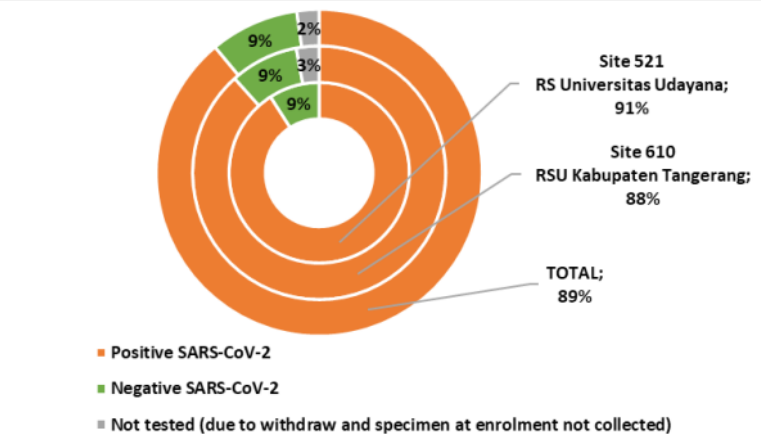
PARTICIPANT STATUS

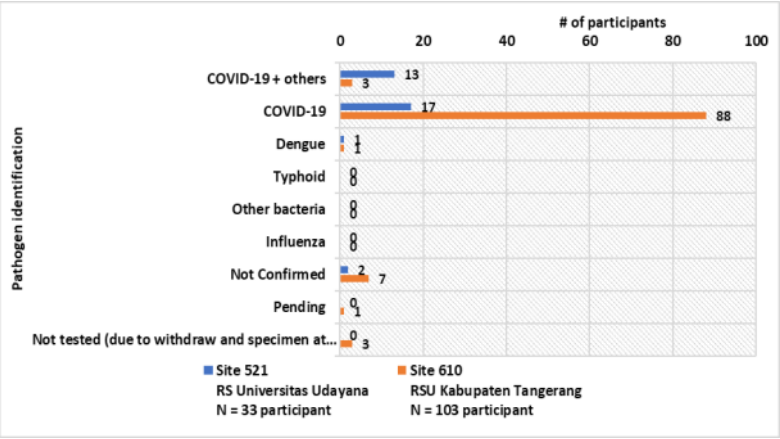
Based on uploaded CRFs as of 5 October 2021, a total of 136 participants were enrolled in ORCHID study, which consisted of 103 participants from site 610 (RSU Kabupaten Tangerang, Tangerang) and 33 participants from site 521 (RS Universitas Udayana, Denpasar). 130 participants (96%) already completed this study, 1 participant passed away during the study, 3 participants withdrew, and 2 participants are still ongoing with the study (figure 1).



Up to 5 October 2021, a total of 121 participants (89%) were identified as positive SARS -CoV-2, and only 12 participants (9%) were identified as negative SARS-CoV-2. 3 participants were not tested due to withdrawal. In site 610, the number of participants identified as positive SARS-CoV-2 was 91 (88%), 9 participants as negative SARS-CoV-2, and 3 participants were not tested due to withdrawal. While in site 521 there were 30 participants (91%) identified as positive SARS-CoV-2 and 3 participants (9%) identified as negative SARS-CoV-2 (figure 2).



Based on pathogen identification data, in site 521, pathogens from 13 participants (39%) are identified as COVID-19 + others, and pathogens from 17 participants (52%) are identified as COVID-19 only. While in site 610, 88 participants' (85%) pathogens are identified as COVID-19 only, following 3 participants (3%) who are identified as COVID-19 + others. 9 participants are not confirmed for any pathogen, consisting of 2 participants in Site 521 and 7 participants in site 610. Only one participant is identified a single infection of Dengue in each site. One participant in site 610 is still pending because we are waiting for other lab test results, and examination cannot be performed for 3 withdrawn participants (figure 3).



The preliminary data at baseline was presented on the Network Steering Committee meeting on 6-7 October 2021. After reviewing the data, several adjustments in clinical data categorization will be made to the available data and further clarification will be processed after the data is cleaned and medically reviewed.

INA-RESPOND Newsletter

ARE DENGUE VACCINES APPROACHING THE FINISH LINE?

By: Herman Kosasih

The emergence of COVID-19 at the end of 2019, and its persistence to this day, has disrupted health services for other endemic diseases such as HIV, tuberculosis, and dengue. All efforts have been focused on controlling the COVID-19 pandemic. Perhaps this is the first time in history that a disease impacts all aspects of life; the information, including hoaxes, is shared and discussed continuously; communities activities are strictly restricted, new habits such as wearing masks, applying disinfectants, social distancing are becoming new norms in the society.

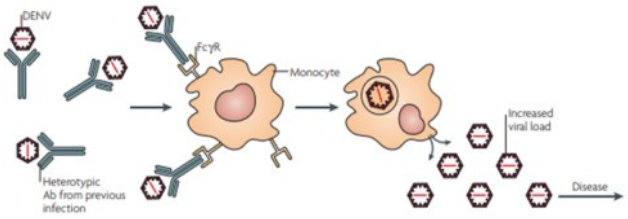
Simultaneously, researchers are racing to discover drugs and vaccines that can defeat this highly transmissible SARS-CoV-2. In less than two years after detecting the virus, various kinds of vaccines have been produced, and as of today, 30% of people in Indonesia have been completely vaccinated. Ironically, HIV, tuberculosis, and dengue researchers are still struggling to find vaccines for the three diseases that have been a burden long before COVID-19 emerged. This year, two HIV vaccine studies were discontinued as they failed to provide sufficient protection to the volunteers. There are 14 vaccines on clinical trials for tuberculosis, and several recent advances are providing fresh hope. However, none of them has been recommended to replace the one-century-old BCG vaccine. With seven vaccines on clinical trials and one vaccine (Dengvaxia) registered, dengue vaccine is the most advanced. However, the mass vaccination campaign of Dengvaxia that started in 2016 in the Philippines caused mistrust and fear in the communities as several children died a few years after vaccination, suggesting a safer and more efficient vaccine is urgently needed.

Dengue in Indonesia

Compared to COVID-19, the reported dengue cases in Indonesia in 2020 were much less (108K vs. 743K, respectively). Similarly, the national mortality rate is lower for dengue than COVID-19 (0.7% vs. 2.8%). However, the incidence of dengue may be underreported during the surge of COVID-19 cases since non-COVID-19 patients are scared to come to health care facilities which at the same time also limit their access for patients. The high prevalence of dengue was shown by INA-RESPOND's AFIRE study, where prior to COVID-19, dengue contributed to 32% of hospitalized febrile illness cases. Another observational adult cohort study also revealed that dengue cases were 43x higher than the government reports due to clinically mild illness in most cases. Therefore they do not seek medical care and diagnostic tests. Dengue outbreaks have occurred several times since it was first discovered in Indonesia in 1968. These outbreaks usually happened every 4-6 years, suggesting immunity from the previous outbreaks had waned. The national mortality rate is currently 0.7%, which is lower in large cities (<0.5%) but higher in areas with fewer medical facilities or resources, such as Maluku (6.5%) in 2020. As vector control implemented for more than 20 years proved unsuccessful, the race to discover safe and efficacious dengue vaccine should continue despite the continuing transmission of SARS-CoV-2.

Dengue vaccine development is challenging due to the pathogenesis

Unlike the COVID-19 vaccine, the dengue vaccine development is much more complicated for several reasons. 1) Despite decades of research on dengue, we still do not have suitable experimental animal models that experience similar pathological features and clinical symptoms as observed in humans for the pre-clinical trials 2) dengue virus has four antigenically different serotypes (DENV1-4). Antibodies produced after the first (primary) dengue infection by a certain serotype have a dual role in controlling DENV infection, either neutralizing or enhancing the entry of the virus. They will provide long-lasting protection against a similar serotype but only short-lived protection against different serotypes (3 months to 2 years). Once antibodies to different serotypes wane, they may facilitate a process known as antibody-dependent enhancement or ADE. These virus-antibody complexes will bind to cells with FcR like macrophages and monocytes -- which are also the target cells of dengue viruses-- through the interaction between FcR on the cell surface and the Fc portion of the antibody. (See fig.1). ADE may also occur after infections with other flavivirus infections such as Zika virus (ZIKV), Yellow fever virus (YFV), Japanese encephalitis virus (JEV), and West Nile virus (WNV). From all these viruses, only JEV is common in certain areas in Indonesia. Besides this FcR entry mechanism, dengue viruses enter macrophages and dendritic cells using DC-SIGN receptors on the surface.



Source: Whitehead, 2007

ADE occurs in 2% of secondary dengue infections with a different serotype, causing dengue vascular permeability syndrome characterized by thrombocytopenia, altered hemostasis, activated complement, elevated level of cytokines, and liver enzyme. Vascular permeability is also caused by the high level of circulating NS1 in the blood vessel. However, most dengue infections result in asymptomatic and mild to moderate clinical outcomes but are associated with a substantial burden of illness.

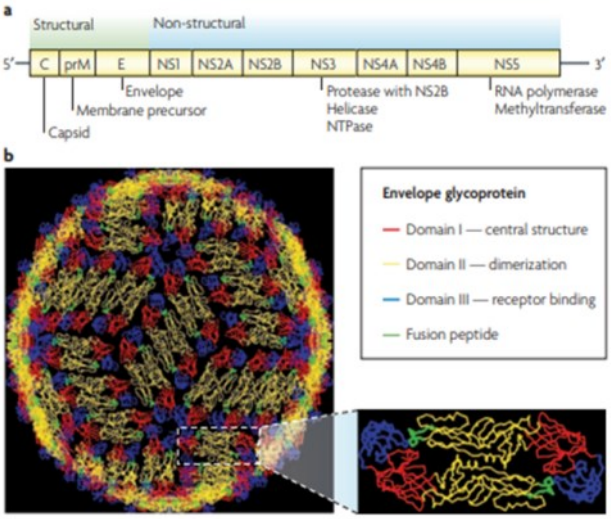
Dengue vaccine: brief history, principles, and clinical trial updates

The search for dengue vaccine was started in the 1940s when DENV-1 that was grown in the mouse brain 32 times and inoculated into susceptible volunteers was not reactogenic but immunogenic and provided protection against challenges with wild-type DENV-1. Although it showed the efficacy of 37% in a trial conducted in 1963 in Puerto Rico, this live mouse brain attenuated dengue vaccine was not continued as concerns regarding possible neurological sensitization and mouse brain tissue adventitious agents were raised. From live mouse brain tissue, researchers from WRAIR, University of Hawaii, and Mahidol University then tried to serially passage (grown) DENV in primary dog kidney, fetal rhesus lung cells, and African green monkey kidney. Unfortunately, they were not successful because it was difficult to find a balance between an acceptable level of reactogenicity and high rates of tetravalent neutralizing antibodies, GMK cells might not be safe, and the response of DENV-3 was too dominant, resulting in the failure of antibodies to other DENV serotypes to raise.

As technology advances, serial passages in cell culture to attenuate dengue virus are replaced with viral chimerization with substituted structural protein genes. In fact, three vaccine candidates on phase 3 trials are chimeric dengue vaccines. Dengvaxia, the leading vaccine produced by Sanofi

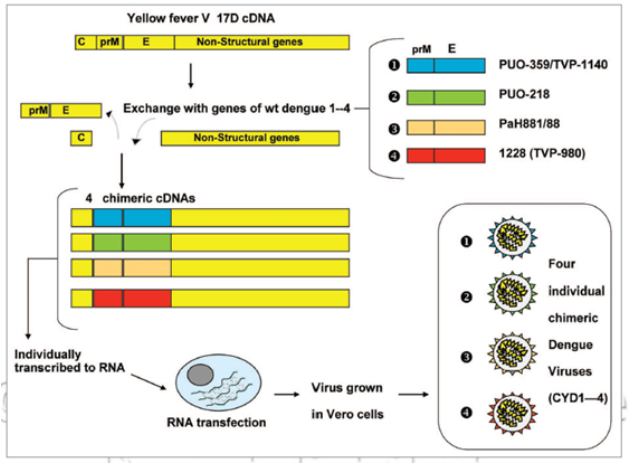
Pasteur, is a tetravalent DENV constructed of chimeras of yellow fever 17D virus and DENV 1-4. In Dengvaxia, the backbone is the yellow fever virus genome, but the pre-membrane and envelope genes are from a certain DENV serotype. After they are produced in Vero-cells, they are combined and given as a tetravalent dengue vaccine. The difference with the second vaccine produced by Takeda (TAK-003) is the backbone. Instead of YFV, Tak003 uses the whole genome DENV-2 as one of the components of the tetravalent DEN vaccine, and three others are a chimera of DEV-2 and the pre-M and E genes of other serotypes. The third is TV003/005, invented by scientists from US-NIAID and the Johns Hopkins Bloomberg School of Public Health. TV003/005 uses whole genomes from 30 nucleotide -deleted (position 172-143 of the 3' untranslated region) DENV-1 and DENV-4, 30 nucleotide-deleted at position 172-143 and 31 nucleotide-deletion at position 258-228 of the 3'UTR DENV-3, and a chimera of a 30 nucleotide-deleted DENV-4 and pre-M and E genes from DENV-2. The illustration of DENV and the structure of these three candidate vaccines are shown in fig.2 and 3.

Besides these chimera vaccines, other DEN vaccines in the development are the recombinant subunit, viral vector, and DNA vaccines. The pipeline of DEN vaccine development is shown in fig.3. Recombinant subunit vaccines are generated mainly using the envelope proteins, the most immunogenic part of DENV. The most promising tetravalent subunit vaccine is V180, produced by Merck, comprising 80% of the envelope proteins from all the serotypes. It has passed the phase 1 clinical trial, showing robust immunogenicity, but antibody titers declined be-

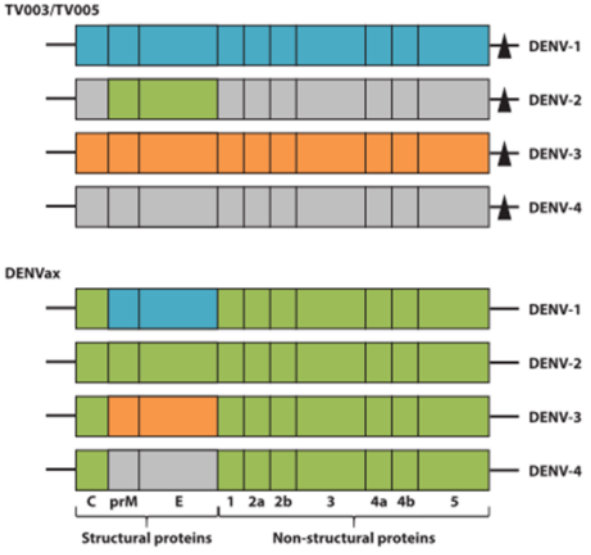


Source: Whitehead, 2007

Fig 2 Dengue Virus (a) the genome (b) details of the envelope glycoprotein covering the virion



Source: Guy, 2010



The structure of three live-attenuated dengue vaccine (a) Dengvaxia, Sanofi Pasteur (b) US-NIAID/Butantan (c) TAK-003, Takeda
Source: Prompetchara, 2020

tween 6-12 months after three doses of vaccines. One of the advantages of this vaccine is a balanced immune response against all DENV serotypes.

Other viruses such as vaccinia virus, adenovirus, and measles virus are used to induce a robust immune response against the expressed foreign antigens. Viral vector vaccine that has reached a phase 1 clinical trial is MV-DEB, a single tetravalent DENV antigen (domain III envelope/EDIII of DENV1-4, and DENV-1 M protein) constructed from a live attenuated measles virus. This vaccine induces both robust neutralizing antibodies and cellular immune responses.

In a DNA vaccine, a partial or full-length gene sequence is cloned and then injected into the skin or muscle. The first DNA vaccine for dengue was developed by the US-NMRC and has reached a phase I clinical trial; however, despite the explored approaches, the immunogenicity of this vaccine remains lower than other vaccine platforms.

The three leading live-attenuated vaccines showed promising results. TAK-003 had an efficacy of 80.2% amongst 20,000 children participants in Asia and Latin America. However, the efficacy against each serotype one year after the final dose was not balanced, 97.7% against DENV-2, 73.3% against DENV-1, and 62.3% against DENV-3, and no conclusion for DENV-4 as too few DENV-4 infections occurred. The highest protection against DENV-2 was not surprising, as the backbone was DENV-2. The lower efficacy for DENV-3 could lead to potential safety problems in baseline seronegative persons, particularly whether the vaccine may increase disease severity in some vaccinees as seen in Dengvaxia, where the efficacy to DENV-2 and DENV-1 was significantly lower (43% and 54.7%) than the efficacy to DEN-3 and DENV-4 (71.6% and 76.9%, respectively). In a study conducted in 10 dengue-endemic countries with 35,000 subjects, although the overall efficacy for symptomatic dengue was 60.3% at 25 months post-vaccination, the hospitalization rate in vaccinated children < 5 years was significantly higher than controls (0.99% vs. 0.2%, p=0.03). After five years of the study, the protection against symptomatic dengue dropped to 34%. ADE was observed in 2-8-year-old seronegative children, among which hospitalization rate was higher (7.1% (137/1928) vs.3.7% (37/1006)), and severe dengue was more frequent (1.6% (30/1928) vs. 0.5% (5/1928). For this reason, Dengvaxia is recommended only for those who already have antibodies against DENV. Similarly, the efficacy of TAK-003 also dropped to 56.2% after two years of vaccination completion, and an increasing rate of hospitalized dengue among seronegative 4-5 years old was observed. However, due to underpowering, it is not significant but still alarming.

The TV Butantan-DV, which is analogous to TV003 of US-NIAID, is on phase III clinical trial. The results

Phase I	Phase II	Phase III	Registration
TDENV-PIV+TDENV-LAV (heterologous prime-boost) by WRAIR **TVDV DNA by NMRC** **V180 recombinant subunit by Merck**	**TDENV-PIV (inactivated) by WRAIR, GSK, Fiocruz**	**TV003/005 Live attenuated by US-NIAID/Butantan** **TAK003 live attenuated by Takeda**	**CYD-TDV live attenuated by Sanofi Pasteur**

Dengue Vaccine Pipeline in clinical trials

from the phase II trial revealed it was safe, with the rash as the most common adverse event, and induced robust, balanced neutralizing antibody responses against all the four DENV serotypes both in naïve and DENV-exposed participants. The seroconversion in both groups were 87% and 81% for DENV -1, 92% and 78% for DENV-2, 76% and 82% for DENV-3, and 89% and 77% for DENV-4. We are now waiting for the results of the ongoing phase III clinical trial in Brazil. This vaccine is expected to be safer and provides a broader protective immune response as it contains non-structural proteins from three DENV serotypes, which is very important as NS1 is associated with vascular permeability.

Combination of a prime-boost vaccine

Like in COVID-19, the use of mixed vaccines in dengue has been thought to improve the effectiveness of one vaccine by another vaccine. The best example is the combination of TAK-003, which is very efficacious against DENV-2 but weak against DENV-3, and no conclusion against DENV-4, with Dengvaxia, which induced high protection against DENV-3 and DEN-4, but low against DENV-2. Other combinations include priming with tetravalent purified formalin-inactivated vaccine and then boosting with a tetravalent live attenuated vaccine, which is now at phase I clinical trial, and the mixed between DNA vaccine and recombinant protein vaccine.

Conclusion

Only Dengvaxia is currently licensed in several countries, but the requirement of pre-vaccination serology tests limits the use of this vaccine. Despite this controversy, it is argued that Dengvaxia, even less-than-ideal, is a valuable vaccine for dengue-endemic areas as it can still have a public health impact. TAK-003 has completed the phase III trial and is applying for licensure. However, a weak immune response to DENV-3 and inconclusive for DENV-4 may still need careful long-term observation to better assess the safety and durability of the vaccine. TV-Butantan-DV is promising as it contains non-structural proteins from three serotypes, which are not available in the other live-attenuated tetravalent vaccine but are very important in the pathogenesis of severe dengue disease. Non-structural proteins are the key targets for T-cell-based immunity, which is essential in controlling the infection. However, the phase III clinical trial is delayed as dengue cases decreased in Brazil due to the Zika virus epidemic. Investigations of other types of vaccines have progressed slowly, and only a few vaccine candidates are in development. Since based on the Dengvaxia experience, ADE could also occur upon poor response to vaccination, and we do not want to see history repeat itself, We still need to wait for an ideal dengue vaccine, which is simultaneously effective against all four serotypes, to come.

Further reading:

1. Gubler DJ, Halstead SB. Is Dengvaxia a useful vaccine for dengue endemic areas? BMJ. 2019;367:l5710.
2. Halstead SB. Is Dengue Vaccine Protection Possible? Clin Infect Dis. 2021.
3. Huang CH, Tsai YT, Wang SF, Wang WH, Chen YH. Dengue vaccine: an update. Expert Rev Anti Infect Ther. 2021:1-8.
4. Kallas EG, Precioso AR, Palacios R, Thome B, Braga PE, Vanni T, et al. Safety and immunogenicity of the tetravalent, live-attenuated dengue vaccine Butantan-DV in adults in Brazil: a two-step, double-blind, randomised placebo-controlled phase 2 trial. Lancet Infect Dis. 2020;20(7):839-50.

INA-RESPOND Newsletter

FROM OUR PARTNER

GOOD PARTICIPATORY PRACTICES FOR THE OUTPATIENT TREATMENT WITH ANTI-CORONAVIRUS IMMUNOGLOBULIN (OTAC) STUDY (INSIGHT 012)

By: Yvette Delph, MBBS, DA

In March of 2021, the Division of Clinical Research (DCR)/National Institute of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH) formed a team to lead the Good Participatory Practices (GPP) initiative for DCR's COVID-19 studies being conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). A GPP Stakeholder Committee was also formed with volunteers from the INSIGHT sites, Statistical and Data Management Center, International Coordinating Centers (ICCs), and the Community Advisory Board, as well as the DCR GPP team.

In consultation with DCR/INSIGHT protocol leadership and GPP stakeholders, the DCR GPP team:

- Determined priorities for each study and across studies
- Defined, secured approval and resources for, and implemented a GPP plan
- Managed the overall GPP process and activities
- Oversaw the design and development of materials and activities
- Oversaw the approval and production of materials and implementation of activities.

The Stakeholder Committee has been instrumental in helping to:

- Determine overarching GPP needs for DCR/ INSIGHT COVID-19 studies
- Assess GPP needs for each protocol
- Develop a GPP plan
- Review GPP materials
- Provide guidance and input on GPP activities

The Outpatient Treatment with Anti-Coronavirus Immunoglobulin (OTAC) Study (INSIGHT 012) is a randomized, double-blind, placebo-controlled clinical trial investigating the safety and efficacy of anti-SARS-CoV-2 hyperimmunoglobulin (hIVIG) for the treatment of adult outpatients early in their infection with COVID-19. The GPP materials and activities prioritized for OTAC focus on study promotion and recruitment, aids to consent, and information for study participants and site staff. All participant-facing materials, including translations, are approved by the central Institutional Review Board (IRB).

Study Promotion and Recruitment Materials and Activities

- **Recruitment Flyer**. A recruitment flyer providing key eligibility criteria and space for sites to customize with contact information and a QR code was produced and translated into 19 languages.

- **Yard Signs** are currently being designed for sites to place outside their facilities indicating that they are conducting OTAC and providing information about the study.

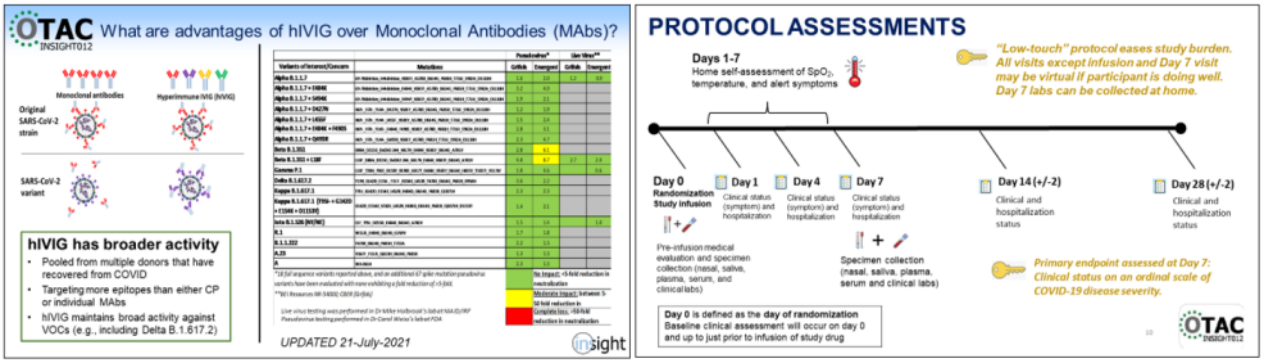


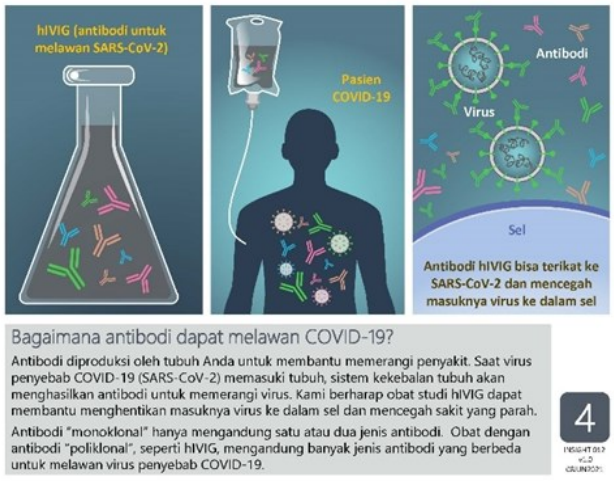
Fig. 2. Sample slides from the OTAC overview presentation

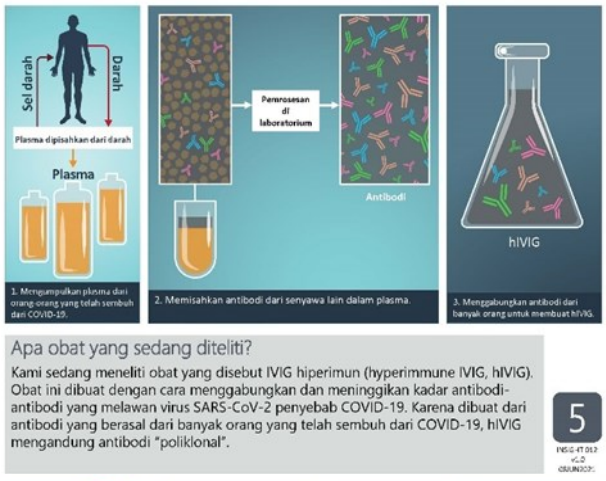
- **Dear Colleague Letter**. A letter was drafted for sites to translate, customize, and send to medical staff in their institutions or colleagues in potential referral facilities providing an overview of OTAC and inviting them to refer interested patients they think may be eligible.
- **Study Overview Presentation**. A slide presentation providing information about OTAC including the scientific rationale, primary objective and endpoint, study design, visit schedule, and information about hIVIG was prepared and updated. This presentation could be used by site investigators to educate site staff as well as to inform faculty members and other colleagues about OTAC.
- **Referral Outreach Program**. This initiative aims to heighten awareness of OTAC at facilities likely to see patients eligible for OTAC (e.g., emergency departments, clinics, COVID-19 testing sites, and physician practices) within the study site's catchment area (40-80 km radius). A vendor identifies potential local referral facilities, and the site investigator approves the list. The vendor, which has been trained on OTAC, contacts the approved facilities via telephone. If the staff at the facility are interested, they are educated about OTAC, and, if they agree, the "Dear Colleague" letter (including the study site address and contact information) and the "OTAC Quick Reference Guide" (described below) are provided to them. The program is designed to minimize the effort required at busy sites and is anticipated to increase referral of potential participants to the local site. A pilot was started at one DCR site; most OTAC sites in the US have expressed interest in using this program and this will be rolled out in the very near future.
- **Videos**. Five-minute videos in English and Spanish providing overviews of OTAC for potential participants and their families/caregivers are currently being developed.
- **Study-specific Web Pages**. Web pages in English and Spanish providing information about OTAC and with links to OTAC informational materials, contacts for inquiries, and site locations and contacts are currently under construction. They will be part of the US Government's Combat COVID website (https://combatcovid.hhs.gov/).

Week of October 2021	Oct 1	Oct 8	Oct 15	Cumulative
Facilities Called (incl. no answers, voice mail, etc.)	47	46	40	**133**
Facilities Educated	10	11	10	**31**
Facilities Agreed to Receive Study Materials	3	4	5	**12**

Table 1. Metrics from the pilot of the OTAC referral outreach program.

Fig. 3. Part of the Combat COVID OTAC web page





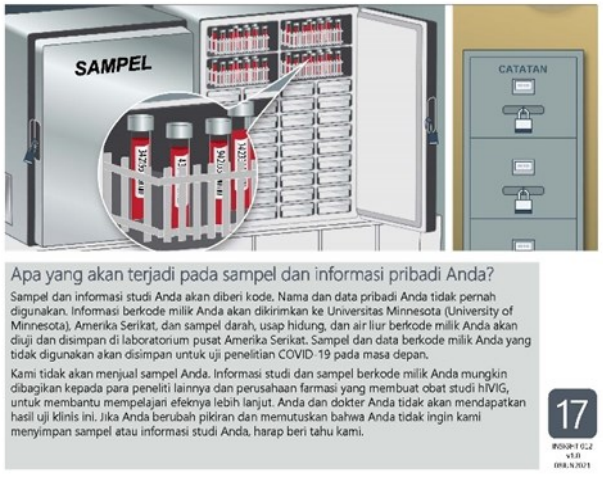


Fig. 4. Select slides from the OTAC Flipbook

- **Combat COVID Call Center**. Visitors to the Combat COVID OTAC web pages will be provided with the opportunity to chat online immediately, call a telephone number, or send an email to get more information about OTAC and have their questions answered. The three red boxes in the image in Fig. 3 will provide these contacts. Inquiries will be directed to a call center that is operated 24/7.

Aids to Consent

- **Flipbooks** are pictorial slide presentations that provide information about OTAC and clinical research in simple language with graphics to illustrate the explanations. OTAC Flipbooks have been produced in digital formats and translated into 18 languages. When sites are registered to OTAC, hard copies in the languages they requested will be printed and shipped to them.

- **Audio Flipbooks**. Audible voice-overs of the PowerPoint slides of the OTAC Flipbook have been produced in English and Spanish.

Information and Tools for Study Participants and Site Staff

- **Instructional Brochure**. Brochures in 20 languages were developed to instruct participants how to take temperature and pulse oximetry measurements at home. They also provide a log for participants to record their readings and instructions on what to do if results are abnormal.
- **Frequently Asked Questions (FAQs) About hIVIG**. Answers to questions site staff may face regarding the use of hIVIG were prepared. Questions answered relate to the potential value of hIVIG, comparison with monoclonal antibodies (mAbs), concomitant use of mAbs, in vitro activity against pseudovirus with mutations of concern, and global relevance of the use of hIVIG.
- **Quick Reference Guide for Site Staff**. A 2-page graphic overview of OTAC was developed to remind site staff about key protocol elements, including study design, schedule of assessments, ordinal scale for clinical status, and eligibility criteria.
- **Screen Failure Log**. To get a better understanding of the reasons why potential participants may not be enrolled, a template screen failure log

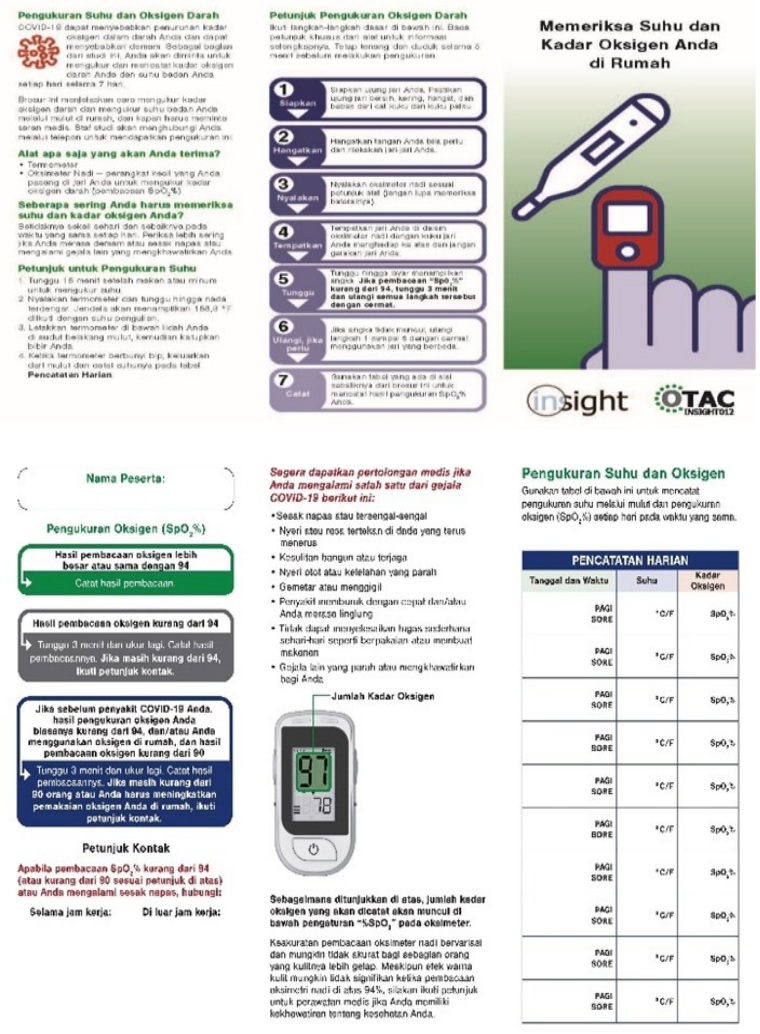


Fig. 5. Instructional brochure on measuring temperature and peripheral oxygen saturation

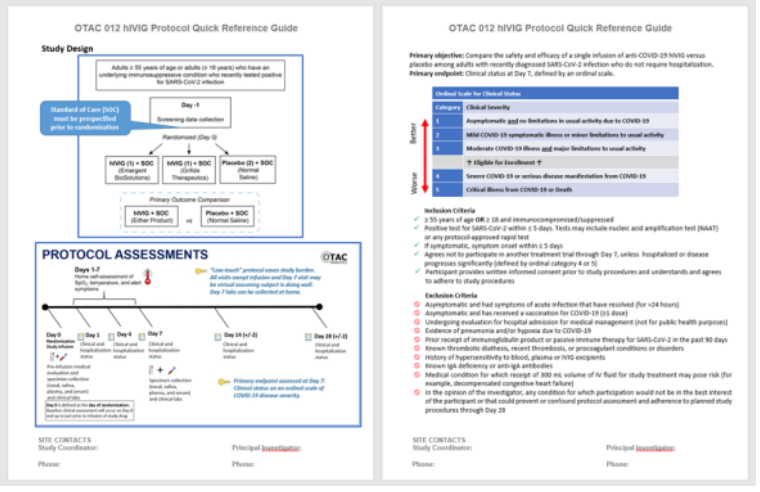


Fig. 6. Quick reference guide for site

Outpatient Treatment with Anti-Coronavirus Immunoglobulin (OTAC) / INSIGHT 012 / Site Number _____								
Screen Failure	**Date**	**Outside 5 Day Window**	**Under 55 but not immuno-compromised**	**Hospitalization imminent**	**COVID-19 not confirmed**	**Exclusionary Co- Morbidity**	**Uninterested in study**	**Other (specify)**
Example	**XX/XX/XXXX**	**1**				**1**		
Screen Failure 1								
Screen Failure 2								

Fig. 7. Screen failure

was developed for site staff to use. The template was circulated to sites in both a printable PDF format and as an Excel spreadsheet that automatically calculates totals for each column.

Electronic Tablets

Interested sites will be furnished with electronic tablets once they are registered to OTAC and provide assurance that they will safely secure and update the tablet. Tablets will provide a user-friendly medium on which potential participants and their families can conveniently view the relevant participant-facing materials listed above. They will be pre-loaded with the materials prior to shipping to sites.

The completed materials discussed above can be downloaded from the INSIGHT website. Additional materials will be posted to the INSIGHT website and to the Combat COVID OTAC webpage when they are finalized.

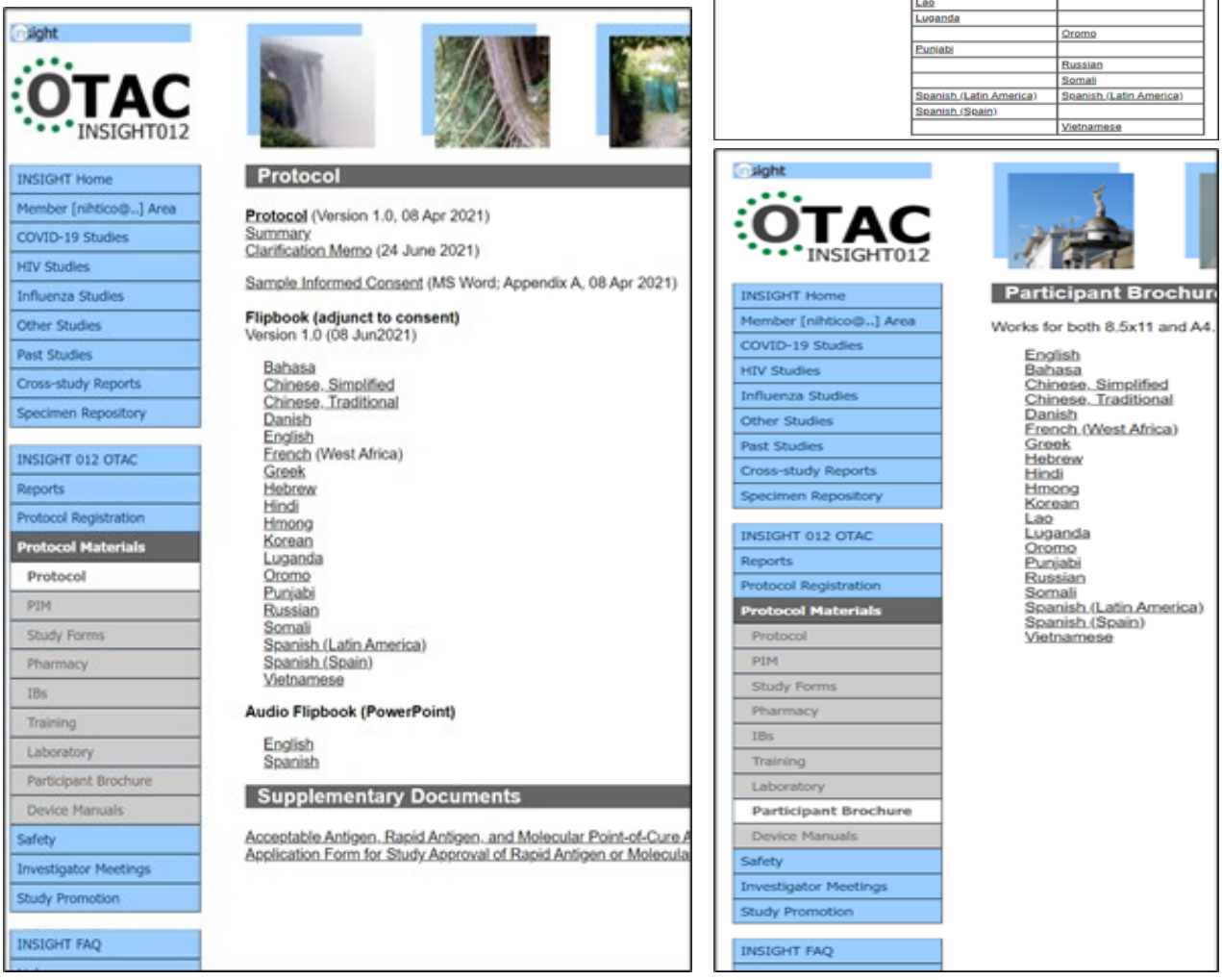


Fig. 8. Location of OTAC GPP materials on the INSIGHT website

INA-RESPOND Newsletter

VITAMIN D DEFICIENCY, ITS EFFECT ON PERFORMANCE, AND HOW TO BOOST IT

By: Maria Lestari

We are currently experiencing a vitamin D deficiency pandemic across the world, especially amongst athletes and the general population, and it seems to be a prominent problem. Athletes have the same predisposition to low levels of vitamin D, most of its concentrations being below 20 ng/mL in a wide range of sports. The recommended daily value (DV) is 800 IU (20 mcg) of vitamin D per day from foods. If you don't get enough sunlight, the intake should likely be closer to 1,000 IU (25 mcg) per day.[1,2]

Vitamin D is important in bone health, but also points out its essential role in extraskeletal functions, including skeletal muscle growth, immune and cardiopulmonary functions, and inflammatory modulation, which influence athletic performance. Vitamin D can also interact with extraskeletal tissues to modulate injury recovery and also influence the risk of infection in both the general and athletic populations.[3]

Over 90% of vitamin D in the human body is formed in the skin tissue influenced by sunlight. It is certain that 25(OH)D can be increased by vitamin D supplementation, proper nutrition and exposing uncovered skin to sun radiation (sun angle should be over 30°). There are many other factors that decrease the level of vitamin D, such as obesity (adiposity may decrease bioavailability of 25-hydroxyvitamin D), liver failure, senectitude, darker skin tone or sunscreen use. Smoking cigarettes also has a significant negative influence on the level of vitamin D. Beyond modifiable factors there are dimensions such as genetic determinants, individual variations or age that are not modifiable. Moreover, a higher rate of vitamin D deficiency occurred especially in post-menopausal women.[5-7]

Vitamin D insufficiency seems to be a very prominent problem amongst athletes and the general population. The evidence available suggests that there is a cause for concern regarding the vitamin D concentration of athletes depending on sun exposure. The results of a huge meta-analysis of 23 studies with 2313 athletes demonstrated that 56% of them had vitamin D inadequacy. Vitamin D insufficiency significantly varied by latitude, also, it was higher during winter and at the beginning of the spring season and for those athletes doing indoor sport activities. The difference between outdoor and indoor athletes is noticeable in the study of Aydin et al., which showed the prevalence of vitamin D deficiency in 59% of outdoor athletes and 64% of indoor athletes.[8,9]

Vitamin D in Sports Performance

Vitamin D supplements can have a positive effect on muscle recovery. In a 2013 study, researchers gave a group of males either 4000 IU per day for 28 days or a placebo before they underwent a strenuous exercise protocol. Subjects who supplemented with vitamin D had a lesser

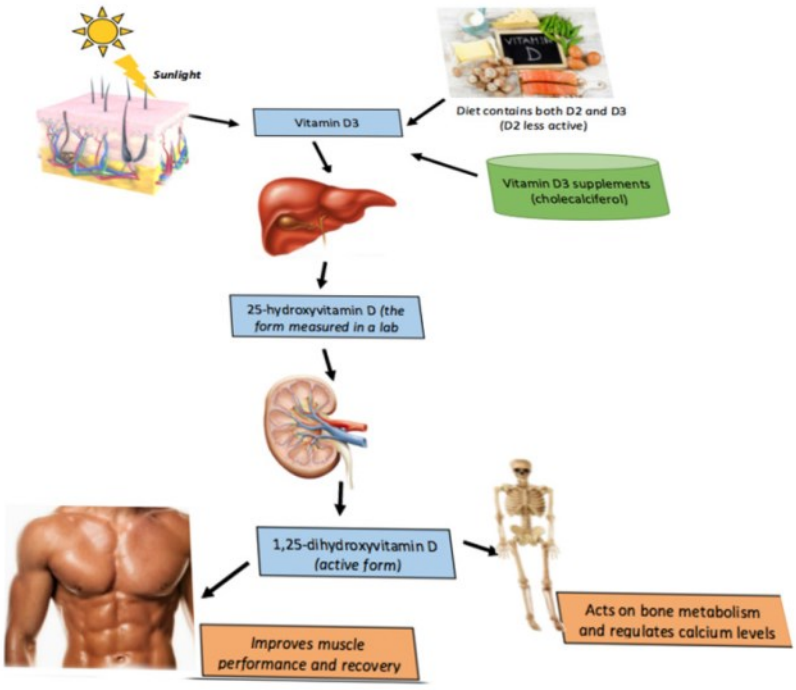


Figure 1.1 Vitamin D Metabolism.[4]

increase in biomarkers associated with muscle damage and soreness than those in the placebo group.[10]

Vitamin D supplementation may have a protective effect against injuries, particularly stress fractures. In a group of female Navy recruits, daily supplementation of just 800 IU vitamin D reduced stress fracture risk by 20%. Similarly, higher intakes of vitamin D in a group of female cross-country runners were associated with a decreased risk of stress fracture.[11,12]

Finally, sufficient levels of vitamin D can have an important knock-on effect by improving post-exercise recovery, possibly by causing an increasing in anti-inflammatory cytokines. Low levels of vitamin D are also associated with an increased risk of illness.[13]

How to Boost Vitamin D

1. Do not miss your exercise

Exercise and a wholesome diet are two important tools on your journey to addressing vitamin D deficiency. According to studies, exercising two to three hours per week boosts the levels of Vitamin D in the body. Regular exercise can also help you maintain a healthy weight and lower the risk of several lifestyle-related disorders.[14]

2. Eat plenty of food that rich in vitamin D

The main sources of dietary vitamin D were fish/fish products followed by eggs, fats/oils, bread/bakery products, and milk/dairy products.[2,15]

Conclusion

Low vitamin D status could negatively impact the health and training efficiency of athletes or people who are active. Research to date suggests that they are at risk for suboptimal vitamin D status, which may increase risks for stress fractures, acute illness, and suboptimal muscle function.

In relation to the prevention of vitamin D deficiency, we must be aware that sun exposure is the main source. Unfortunately, there is evidence concerned about the possibility that sun exposure, if uncontrolled, may promote skin cancer. On the other hand, we must also take account nutrition in active people and vitamin D. A personalized nutrition plan should develop. Sufficiency of essential minerals and micronutrients, like magnesium, are critical to enhancing activation of vitamin D.

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KNOWLEDGE BROKER – IS IT FOR US?

By: Aly Diana

COMIC CORNER

As a scientist, do we routinely notice opportunities for research to be translated into tangible benefits for society? Do we believe that science often fails to benefit from what society has to offer? Do we sometimes feel frustrated that the decision makers and scientists somehow speak a different language? If we answer 'yes' to these questions, and we are someone who have extra passion and patient, enjoys explaining research to non-scientists, bringing people together from diverse professional backgrounds, and acting as a facilitator, then a career in an emerging area—knowledge brokering—could be an excellent choice for us. But what exactly is a knowledge broker?

A knowledge broker is a person who promotes interaction between researchers and end users, as well as to develop capacity for evidence-informed decision making. A knowledge broker provides a link between research producers and end users by developing a mutual understanding of goals and cultures, collaborates with end users to identify issues and problems for which solutions are required, and facilitates the identification, access,

assessment, interpretation, and translation of research evidence into local policy and practice.

To achieve this, knowledge brokers build and sustain productive working relationships with a range of stakeholders, be they individuals or organisations, to understand their existing knowledge base and capacity for evidence-based decision-making and to subsequently help build these. Underpinning this is the extent to which knowledge brokers are perceived by their stakeholders as relevant, legitimate, and credible – which requires knowledge brokers to not only have an in-depth understanding of the science that they are to communicate, but also a strong understanding of the stakeholders they engage with, their operational environment, and the most appropriate avenues to influence the research and how it is conducted. In turn, knowledge brokers must also have the ability to interpret and frame stakeholder needs and then communicate those to the research community. Finally, for knowledge brokers to act efficiently it is widely believed that they must possess superior interpersonal, communication, and motivational skills.

The knowledge broker is expected to be a skilled facilitator who built trust by their open stance, neutrality, and knowledge of research and policy contexts. Key functions of knowledge brokers included eliciting and clarifying information, linking the review questions to the context and purpose, moving fluidly between policy and research perspectives, and weighing up review options against policy objectives.

Thus, while knowledge brokering roles present a number of challenges, when operating effectively knowledge brokers are believed to have the ability to facilitate organisational change by 1) removing barriers to evidence-based decision-making, 2) promoting a culture that values the use of the best available science in policy and practice, and 3) influencing science so that it is appropriate to stakeholder needs.

So, would us be interested to be a knowledge broker? Good luck for us!

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