INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

November 2019

Lifestyle and Sports
More Muscles for
A longer and Better life

Comic Corner
MY INTEGRITY,
MY PRIDE

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TRIPOD and INA-PROACTIVE
Studies' Updates

NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2019

INA-RESPOND Steering Committee Meeting,
13—14 Nov 2019, Jakarta

INA-RESPOND newsletter

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MASTHEAD

INA-RESPOND Newsletter

TRIPOD & INA-PROACTIVE Study Updates

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

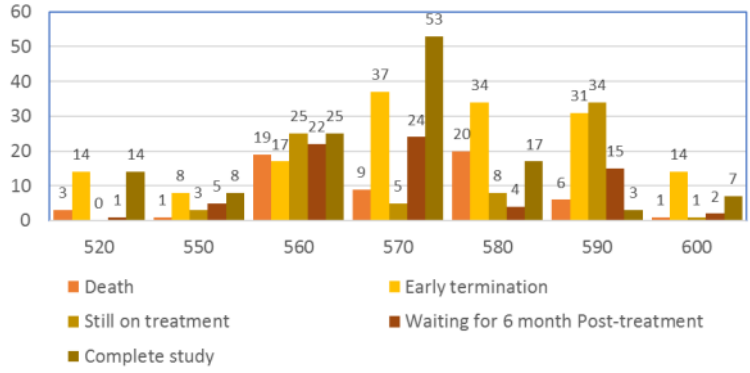

Figure 1.Participant status per site based on uploaded CRF per 31 Oct 2019

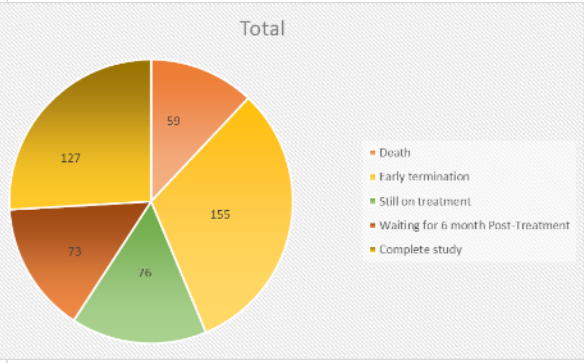

Figure 2. Total Participants Status based on uploaded CRF per 31 Oct 2019

STUDY UPDATES

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PARTICIPANT STATUS

Per 31 October 2019, the total ongoing participants in TRIPOD study are 149 out of 490 enrolled participants. From those 149 current participants, 76 are still on TB treatment while 73 are waiting for 6-month post-treatment visit. One hundred twenty seven participants have completed the study while 214 participants are terminated early (including death). Therefore, there are still 30.4 % participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, there are 1 participants from site 520 (RS Sanglah Denpasar) who still need to be followed up, eight participants from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar), 47 participants from site 560 (RSUP dr. Kariadi Semarang), 29 participants from site 570 (RSUD dr. Soetomo Surabaya), 12 participants from site 580 (RSUP dr. Sardjito Jogjakarta), 49 participants from site 590 (RSUP Persahabatan Jakarta), and three participants from site 600 (RSUP dr. Adam Malik Medan).

AWAITING CULTURE AND DST RESULT

The result for baseline culture and DST from all sites is complete. However, we are still waiting for the culture isolate date from nine subjects.

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 (still waiting for culture isolate date from 9 subjects)
570 (n=128)	Complete	Complete
580 (n=83)	Complete	Complete
590 (n=89)	Complete	Complete
600 (n=25)	Complete	Complete

Figure 3.Culture and DST results up to 31 Oct 2019

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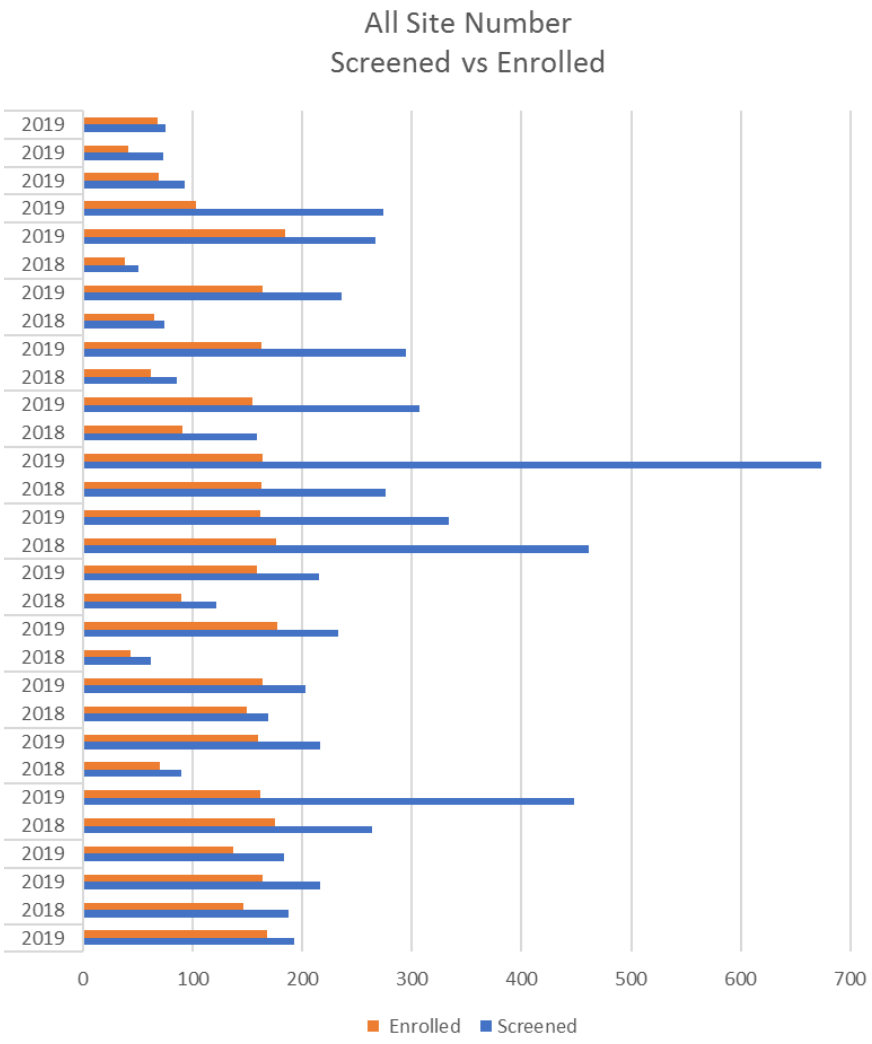
On 5 Nov 2019, one new site was activated as site number 19 in PROACTIVE Study. That site is site 520 (RSUP Sanglah, Denpasar). The Site had its first subject enrolled on 7 Nov 2019 and will continue to recruit the eligible subject until Jun 2020.

Screening and enrollment activities are still ongoing at seven sites. By 3 Nov 2019, a total of 3,831 subjects had been enrolled, consisting of 3,663 adult and 168 pediatrics from a total of 6,532 subjects screened. The enrollment rate was 58.64% from total screening. The number of screened and enrolled subject from each site is shown in figure on the right.

The total end of study and existing subject as of 3 Nov 2019 is shown in figure 2.

A Site visit was done on 29 – 31 Oct 2019 to RSUD Dr. H. Moch. Ansari Saleh, Banjarmasin as the third Site Monitoring Visit. Monitoring Visit will also be conducted to Site 580, RSUP dr. Sardjito Hospital, Yogyakarta on 18 – 20 Nov 2019 as the third Monitoring Visit and to Site 670, RSUD Zainoel Abidin Aceh on 10 – 11 Dec 2019 as the second monitoring visit.

While for site 520 RSUP Sanglah, Denpasar, its first Monitoring Visit is planned on 3 – 4 Dec 2019. Hopefully, the activation of site 520 - RSUP Sanglah Hospital as the last study site may enrich the data and coverage of this study to represent Indonesia HIV population in INA-PROACTIVE Study.



Site Number	Subject		Total End Of Study	Total Existing Subject
	Total Screened	Total Enrolled		
510	192	168	0	168
530	403	310	6	304
540	183	137	0	137
550	712	337	13	324
560	306	230	7	223
570	372	313	1	312
580	295	220	0	220
590	336	249	15	234
600	795	338	9	329
610	950	327	9	318
630	466	245	1	244
640	380	225	0	225
650	310	229	4	225
660	317	222	1	221
670	274	103	0	103
680	93	69	0	69
690	73	41	1	40
700	75	68	1	67
Grand Total	6532	3831	68	3763

INA-RESPOND Newsletter

SITE PROFILE

ABDUL WAHAB SJAHRANIE GENERAL HOSPITAL , SAMARINDA

By: dr. Dewi Paramita Yuniarahmi

Abdul Wahab Sjahranie General Hospital (AWS) is one of the referral hospitals in Samarinda, the capital city of Kalimantan Timur. AWS was activated as INA-RESPOND's network (assigned as site 660) on October 2, 2018. The site is led by Dr. dr. Carta Agrawanto Gunawan, Sp.PD, K-PTI, FINASIM as the Site PI. Our study team has 3 Co-PIs (Dr.dr.Sunarto Ang, M.Sc.,Dipl.Immunology; dr. Hendra,Sp.A; and dr.Sri Wahyunie,M.Kes,Sp.PK). They are assisted by two Research Assistants (dr. Dewi Paramita Yuniarahmi and dr. Yusuf Taqwa Muladi), two Laboratory Technicians (Monika Lestari Palondongan, A.Md.AK and Heniastuti, A.Md.AK), two study nurses (Ns Nursiah Mukano,S.Kep and Ady Achmaddany,A.Md.Kep), and 1 phlebotomist (Sudibiyantoro,S.Kep,Ns, M.Kes). We hope that our contribution to this INA-RESPOND research will be beneficial for the health community. Here are the short profiles of each member of our study team:

Dr. dr. Carta Agrawanto Gunawan, Sp.PD, K-PTI, FINASIM is our Site PI in PROACTIVE Study. He is a very inspiring person who likes writing journals and contributing to Tropical Medicine Conference. Besides his position as Principal of Medical Research Ethics Committee in AWS, he also takes part in teaching staff in Medical Faculty of Mulawarman University. As Site PI, Dr. Carta hopes by taking part in research will give contributions to science development especially HIV disease in Kalimantan Timur.

Dr. dr. Sunarto Ang, M.Sc., Dipl.Immunology is one of our Co-PIs who is very excited about this research. He takes part in national HIV/TB program, and he is also a trainer of HIV/TB Program for healthcare facilities that run this program in Kalimantan Timur. He reads and frequently shares research journals to our team, especially journals about HIV/TB and molecular research.

dr. Sri Wahyunie, M.Kes, Sp.PK, who was graduated from Hasanuddin University, works as a Clinical Pathology staff in AWS. She is a very motherly Co-PI who always encourages Research Assistants (RA) to learn how to run good research by actively taking part in INA-RESPOND's study. She often gives guidance to RA & Laboratory Technicians whenever we face problems in the laboratory.

dr. Hendra, Sp.A is responsible for the perinatology division and HIV program in our hospital. Besides his job as a pediatrician and teaching staff, he often gives presentations in seminars. He cares about his patients and doesn't hesitate to help them directly.

dr. Dewi Paramita Yuniarahmi, as the first RA at site 660, holds a vital role in site activation. Even though she doesn't have many experiences in research, she runs her role excitedly along with all team members.

dr. Yusuf Taqwa Muladi is the second RA in site 660. As a doctor who has just finished his internship program, he hopes he can be of help for the first RA to complete the tasks required by the study. He wishes that could obtain precious experiences by joining the study team, and perhaps continue his education in internal medicine.

INA-RESPOND Newsletter

DENGUE VIRAL INFECTION IN INDONESIA

By: Dr. I Made Susila Utama, SpPD-KPTI

PUBLISHED RESULTS

Dengue viral infection in Indonesia: Epidemiology, diagnostic challenges, and mutations from an observational cohort study

https://www.ncbi.nlm.nih.gov/pubmed/31634352

The AFIRE Study is the first multicenter observational cohort study of the INA-RESPOND network involving eight sites in Bandung, Bali, Semarang, Jogjakarta, Surabaya, Makassar, and Jakarta (RSCM and Sulianti Saroso). A total of 1,486 study participants were enrolled, both adults and children, to look for causes of acute fever requiring hospitalization. Clinical information and specimens were collected at enrollment, 14-28 days, and three months. The most common cause is dengue virus infection (31.9%) confirmed by referral laboratory assays. In terms of diagnosis accuracy, 414 (88.5%) of 468 cases were accurate in diagnosis, but 54 cases that were not diagnosed with dengue turned out to be a dengue virus infection. On the other hand, there were 100 cases initially diagnosed with dengue infection but were finally classified as 'non-dengue' because they could not be confirmed by the referral laboratory. The mortality of dengue virus infection was relatively low (0.6%). Most had a history of previous dengue infection (92.3%). Dengue virus is found throughout the year in all study sites, with higher incidence from January to March. DENV-3 and DENV-1 were the most identified serotypes. In mutation analysis, the study identified the DENV-1 virus with TS13 (A-G), TS113 (G-A), TS116 (C-T), and TS119 (C-T) substitution in the serotyping primer annealing site (nucleotide 568-586).

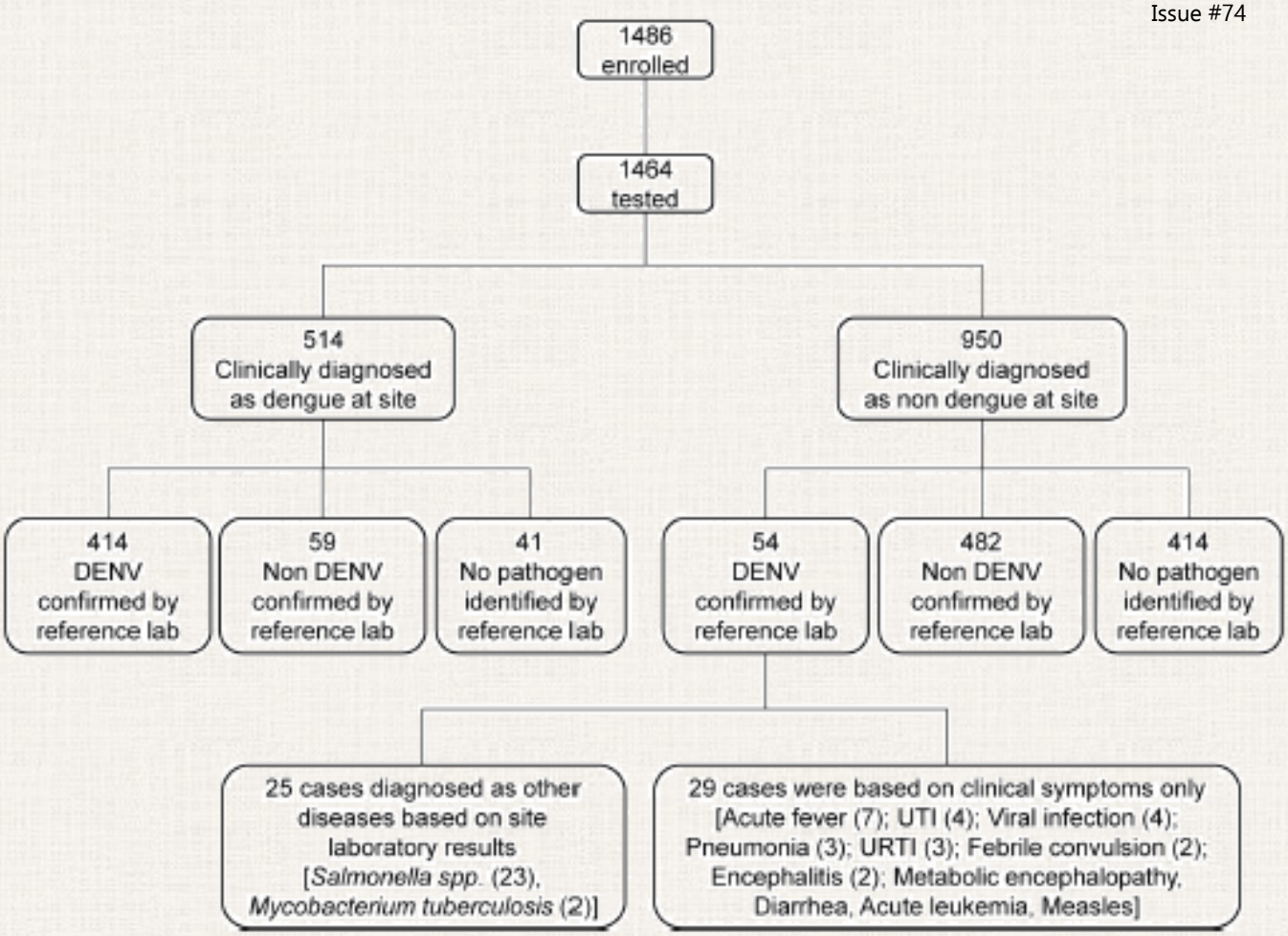


Fig 4. Clinical diagnoses and reference lab confirmation of DENV infections. Presumed etiologies of missed DENV infections and actual etiologies of incorrectly presumed DENV infections are shown. Reference laboratory diagnosis was considered the true diagnosis.

The picture above compares the clinical diagnoses at the study sites with the test results done by the referral laboratory. The accuracy of the diagnosis of dengue infection is vital because misdiagnosis will negatively impact the treatment and outcome. Clinicians should use algorithms to confirm the diagnosis and develop laboratory capacity in diagnosing dengue infection.

The pictures below show the geographical distribution of dengue cases in various sites (left). The distribution of monthly cases shows an increase in January-March (right).

The opportunity to be involved in multicenter research like this is beneficial for everyone involved in the study. The study team gets the chance to learn to do research following a well-structured protocol, discuss and learn from senior researchers from various sites, attend workshops and training, and publish journals. We sincerely thank INA-RESPOND, especially to dr. M. Karyana, M.Kes, Prof. DR. Dr. Tuti Parwati Merati, SpPD-KPTI (Steering Committee member at Bali site), Dr. Herman Kosasih, and all staff at INA-RESPOND Secretariat for making this moment come true; the results of this dengue study are finally published in an international journal. The results of this study were also presented at the WCIM (World Congress of Internal Medicine) in Cape Town, South Africa, in October 2018, supported by INA-RESPOND. Hopefully, in the future INA-RESPOND will further develop and produce quality research recognized on an international scale while continuing to build the capacity of health research in Indonesia.

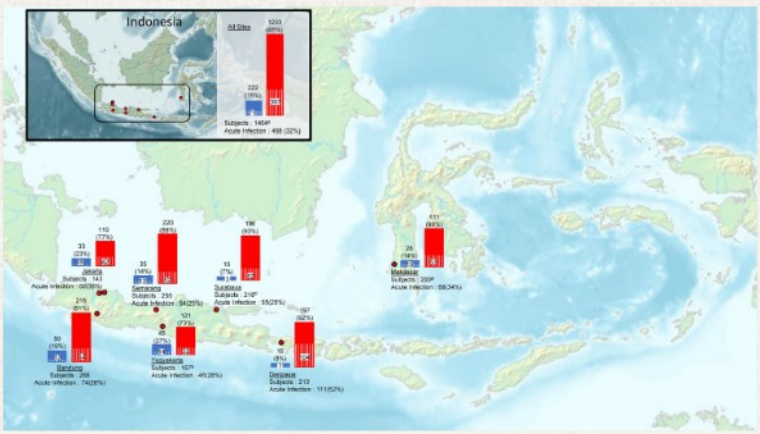


Fig 1. Geographic distribution and rates of DENV cases. Red dots show study site location. The number of fever cases and acute Dengue infections (percent) at each site are shown below the site name. Bars show the proportion of patients with (red bars) and without (blue bars) prior exposure; white stripes pattern inside the bars shows the subset who experienced acute infection. Note: Nine subjects* had no acute specimens for exposure prior to enrollment: 1 subject in Yogyakarta[a], 7 subjects in Surabaya[a], and 1 subject in Makassar[a]. Map source: Wikimedia Commons Atlas of the World [*Atlas of Indonesia*]. Available from: https://commons.wikimedia.org/wiki/Atlas_of_Indonesia#/media/File:Map_of_Indonesia_Demis.png [Accessed 23 September 2019].

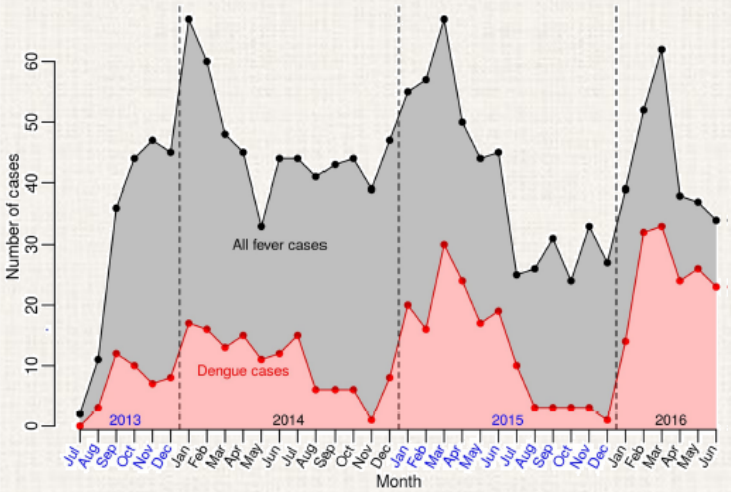


Fig 2. Dengue cases per month. Red dots/area: dengue cases. Black dots/gray area: all fever cases.

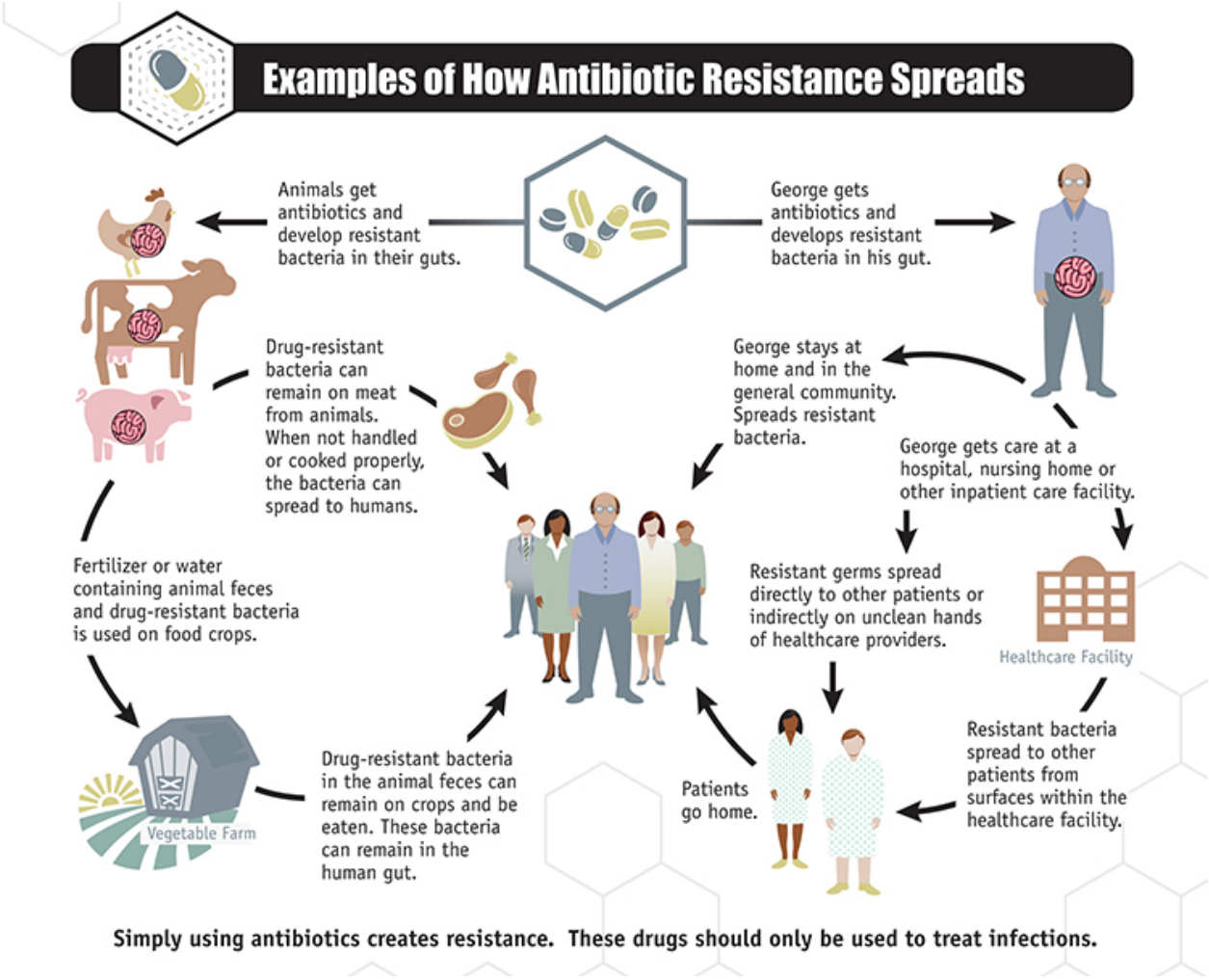
https://doi.org/10.1371/journal.pntd.0007785.g002

INA-RESPOND Newsletter

FROM OUR SPONSOR

WHAT IS ANTIMICROBIAL "RESISTANCE" AND ITS IMPACT ON PATIENT OUTCOMES?

By: John H Powers MD



Simply using antibiotics creates resistance. These drugs should only be used to treat infections.

The term "antimicrobial resistance" refers to decreased effectiveness on patient outcomes of currently available therapies to treat infectious diseases. While the primary focus should be on patient-centered outcomes such as survival, patient symptoms and function in their daily lives, in practice "resistance" often is defined as the amount of drug in a test tube (in vitro) needed to inhibit the growth of microorganisms – the minimum inhibitory concentration (MIC). This artificial environment does not take into account patient factors and the important contribution of the host immune system on patient outcomes especially in serious infectious diseases

Patient factors affecting outcomes in infectious diseases is common. The earliest data on the use of penicillin for pneumococcal pneumonia showed marked differences in the benefits of the drug based on patient demographics. While older patients die more often, the treatment effect of penicillin (the difference between penicillin treatment vs standard supportive care at the time) was much larger in older, sicker patients than in younger, healthier, patients.[1] Conversely, more recent data showed that in a meta-analysis showing increased mortality with tigecycline compared to older effective therapies demonstrated that the effects of tigecycline were numerically worse in patients who were sicker and infected with resistant pathogens compared to studies enrolling younger, healthier persons with susceptible pathogens.[2]

Controlling for patient factors and severity of illness is important in evaluating the impact of antimicrobial resistance on patient outcomes, as patients with resistant organisms are on average older and sicker than patients infected with susceptible organisms. In a recent study of patients with Staphylococcus aureus blood stream infections (BSI), crude mortality was higher in patients infected with methicillin-resistant (MRSA) compared to methicillin-susceptible (MSSA) organisms. However, after controlling for patient factors and baseline severity of illness, there was no difference in mortality between patients with MRSA and MSSA BSIs, showing that differences in mortality were due to patient factors and not in vitro resistance.[3] Studies showing that patients with resistant organisms die more often that do not attempt to control for these confounding factors may be comparing older, sicker patients to younger healthier patients and thus do not measure the impact of in vitro resistance on outcomes. Therefore, it often is challenging for determine whether patients die from antimicrobial resistance or with antimicrobial resistance but with other factors more influential in patient outcomes.

Furthermore, the effects of drugs on the host immune system or drug adverse effects may be as important or more important than the effects of the drugs on microorganisms. There may be important differences between drugs even when organisms are susceptible in vitro to both drugs. This was demonstrated recently in the randomized MERINO trial enrolling patients with extended spectrum beta-lactamase producing E.coli and Klebsiella BSIs. Despite susceptibility to both drugs meropenem improved survival by 8.5% on average compared to piperacillin-tazobactam. Even with this mortality difference, there was no difference in the biomarkers of clearance of bacteria from the blood, fever, or peripheral white blood cell count. This study shows why new drugs need to be studied in randomized trials to evaluate patient outcomes and the dangers of "medicine by MIC" or relying on biomarkers as surrogate endpoints in trials rather than directly measuring patient outcomes such as survival, function or symptoms.

How in vitro antimicrobial resistance is defined and categorized also is important. Patients do not ask about how many drugs will not work for them but rather want to know if there is an effective drug to treat their disease. However, "multidrug" resistance has been defined in terms of how many potentially drugs have decreased in vitro biological activity regardless of how many effective drugs for treatment remain. NIH investigators have attempted to address this by defining a new term – "difficult to treat" resistance (DTR) – defined as patients whose disease is caused by organisms resistant to all first line, less toxic agents such as beta-lactams and quinolones. This places the focus on how many remaining potentially less effective or more toxic alternatives remain.[4]

John H Powers MD

Director of Collaborative Research,

All these factors have important implications for future research. Susceptibility criteria for drugs should be based on patient outcomes and not MICs or pharmacokinetic/pharmacodynamics parameters alone. Studies to evaluate the impact of resistance on patient outcomes should use control groups of patients with susceptible infections (not uninfected patients) and should attempt to control for patient factors and baseline severity of illness (realizing that unmeasured confounding may still remain). Resistance should be defined in a way that makes clinical sense with a focus on remaining effective drugs. And most importantly, studied on new therapies should be randomized superiority trials in the target population of patients with few or no options using patient centered outcomes to most accurately and ethically evaluate the benefits and harms of new drugs.[5]

REFERENCES

1. Fleming TR, Powers JH. Issues in noninferiority trials: the evidence in community-acquired pneumonia. Clin Infect Dis 2008;47 Suppl 3:S108-20.

2. Prasad P, Sun J, Danner RL, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis 2012;54:1699-709.

3. Yaw LK, Robinson JO, Ho KM. A comparison of long-term outcomes after meticillin-resistant and meticillin-sensitive Staphylococcus aureus bacteraemia: an observational cohort study. Lancet Infect Dis 2014;14:967-75.

4. Kadri SS, Adjemian J, Lai YL, et al. Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents. Clin Infect Dis 2018.

5. Powers JH, Evans SR, Kesselheim AS. Studying new antibiotics for multidrug resistant infections: are today's patients paying for unproved future benefits? BMJ 2018;360:k587.

INA-RESPOND Newsletter

MY INTEGRITY, MY PRIDE

By: Aly Diana

COMIC CORNER

"When we take responsibility for the work we produce, we give it credibility. Without credibility, there is no point in doing the work."

-Deb Eerkes-

Academic integrity is a significant value that should be committed by all involved in academic discourse. It is the moral code that builds trust between scholars and allows the academic community to develop and improve. We have to admit that we build our ideas based on other ideas and previous research/studies. There is no secret here. Without academic integrity, everything that we do in our capacities as teachers, learners, and researchers loses value and becomes suspect. Therefore, in this digital world, with almost unlimited access to information, following academic integrity means not only protecting others but also ourselves.

In general, the topic of academic integrity is usually framed around misconduct and dishonesty, carrying both negative and punitive connotations. However, it is more important to shift the dialogue towards an approach that is more educative, preventative, and positive. We need to build the right environment to thrive together in which ethical standards are upheld. The Fundamental Values Project is an attempt to frame academic integrity in ways that are both positive and pragmatic. The International Center for Academic Integrity (ICAI) promotes academic integrity as a commitment to six fundamental values: honesty, trust, fairness, respect, responsibility, and courage.

When the fundamental values are embraced, utilized, and put into practice, they become touchstones for scholarly communities of integrity. And to make it happen, while there is no "one-size-fits-all" formula for establishing climates of integrity, there are some steps that can be taken by institutions to maximize chances for success, which include: 1. Develop and publicize clear, fair, academic integrity policies, procedures, and statements that can be adequately understood and consistently implemented; 2. Promote positive aspects of academic integrity; 3. Educate all members of the community; 4. Practice the actions described consistently and fairly. Provide support to those who follow the policies and uphold standards; 5. Develop, explain, and administer equitable, transparent systems for adjudicating integrity violations; 6. Stay abreast of current developments in technology and educational practices to anticipate increased risks and address potential problems; 7. Regularly assess the effectiveness of academic integrity policies, procedures, and practices. Revise and revitalize as necessary to update and improve.

The wonderful news is that the Indonesian government through Ministry of Research, Technology, and Higher Education of the Republic of Indonesia has shown that we are on the right track in following international recommendations and beyond. In 2019, the ministry introduced ANJANI (Anjungan Integritas Akademik Indonesia – Indonesian Academic Integrity Platform; http://anjani.ristekdikti.go.id/integritas-akademik/). This platform provides the values, guidelines to measure academic integrity, sanctions/consequences, and procedures to report misconduct cases.

Our government has shown its efforts to build the right environment to promote a healthy academic environment. Let's contribute by following the six fundamental values and sharing them. Another consideration, please also remember that our studies might be used as a foundation for developing policies. Only studies conducted with integrity can lead to good policies.

REFERENCES

Ministry of Research, Technology, and Higher Education of the Republic of Indonesia. 2019. ANJANI (Anjungan Integritas Akademik Indonesia). http://anjani.ristekdikti.go.id/integritas-akademik/

International Center for Academic Integrity. 2017. https://www.academicintegrity.org/

UC Berkeley. Center for Teaching and Learning. 2019. Academic Integrity. https://teaching.berkeley.edu/resources/design/academic-integrity

Lutter College. 2019. What is Academic Integrity? https://www.luther.edu/academic-integrity/about/

Piascik P, Brazeau, GA. 2010. Promoting a Culture of Academic Integrity. Am J Pham Educ; 74(6): 113.

INA-RESPOND Newsletter

MORE MUSCLES FOR A LONGER AND BETTER LIFE

By: Edrick Purnomo Putra

Aging is something that humans cannot avoid. It is a very complex process associated with multiple changes in the human body as our age increases.[1] These changes occur not only in the mind, but also in the body. A lot of research was conducted to find out what is happening when we age and ways to prevent or slow it down in hope of getting a greater life span. Factors like genetics, lifestyle, specific diet, social and mental health were explored to find the results. Global Health Observatory (GHO) Data from WHO stated that global life expectancy rate in 2016 was 72,0 years (74,2 years for females and 69,8 in males), ranging from 61,2 years in the African region to 77.5 years in the European region, giving a ratio of 1.3 between the two regions. The number increased by 5.5 years between 2000 and 2016.[2]

Research on body composition changes related to aging is very intriguing. These changes could potentially be the culprit in making us sick or prematurely die when we get older. Therefore, a lot of research on body composition changes in aging related to longevity or mortality was conducted. Commonly, we use Body Mass Index (BMI) to measure our body composition. A cohort study of 3.6 million adults in the UK published in 2018 concluded that BMI has J-shaped associations to overall mortality and the most specific cause of death. While the results show that obese people have higher hazard ratio of mortality, we must not forget that too low BMI could also impose risk. Even in some specific causes like mental and behavioral, neurological, and external causes, lower BMI was associated with increased mortality risk.[3]

Now, the question is, can BMI become a precise value in examining a person's body composition? Unfortunately, not. BMI could be used in population or community settings, yet it is still not precise enough to be used in a personal clinical setting. In a three compartmental model, our body composition can be roughly divided into the fat mass, bone mass, and lean body/muscle mass.1 Body composition measurements can be done by using many modalities, which include anthropometry measurements, dual-energy x-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), ultrasonography, computer-

ized tomography (CT) and magnetic resonance imaging (MRI). Each measurement has its advantages and disadvantages, and choosing modality also depends on the accessibility of the modality. DXA is considered the best method in clinical practice and proposed as the new gold standard of body composition analysis, while BIA is more accessible and easier for more people.[4]

We all agree that higher visceral adiposity, usually implied in BMI measurement, could be harmful to the body. Unfortunately, we often overlook the role of muscle mass. In contrary to the hazardous effect of adiposity, muscle mass has opposite effects on our body. Higher muscle mass might be beneficial for our overall health. Muscle mass index was inversely associated with all-cause mortality in a 10-16 year follow up study published in NIH in 2014.5 People with too low muscle mass, also in people with low BMI, have higher risk of mortality. Prospective research in Brazil involving 839 elderly published in 2019 concluded that low muscle mass both in men and women significantly increased all-cause mortality risk and cardiovascular mortality in elderly.[1]

We may not realize that our muscle is decreasing as we age. A study about skeletal muscle mass examined using MRI in Canada involving 468 men and women aged 18-88 years old shows that relative muscle mass starts decreasing in the third decade. However, a noticeable decrease in absolute muscle mass was not evident until the end of fifth decade. This decrease was primarily attributed to a decrease in lower body muscle.[6] A condition called sarcopenia is described as an age-related loss of skeletal muscle mass in elderly. It is a well-established factor associated with the decreases in muscle strength and difficulty in mobility.[7] Factors like certain illness, sedentary behavior in older age, and reduced responsiveness of tropic hormones like androgens and growth hormones were proposed as the cause of muscle loss in elderly.[6] Loss of muscle mass appears to precede loss of bone mass during physical inactivity caused by mechanical unloading, and it increases the risk of developing osteoporosis.[7]

Other than muscle mass, muscle strength is also an important factor. Muscle weakness is associated with some negative outcomes, including physical function limitation, disability, and multimorbidity.[8] One of the easiest and cost-effective measurements of muscle strength is hand grip strength measured by dynamometer. It can be a reliable alternative to measure overall muscle strength and a prognostic indicator of subsequent functional limitations and future disease status, especially in the elderly.[9] Research done by Duchowny by using the National Health and Retirement Study data in U.S. found that 46% of elderly were considered weak at the baseline and concluded that muscle weakness, measured by handgrip strength, is a key risk factor for premature mortality among older Americans.[8] In another study, Duchowny also measured changes in activities of daily living (ADL) across a two-year period and found that the odds of experiencing an onset of ADL disability was 54% higher among weak individuals compared to those who were not weak at baseline and also the odds of experiencing a progression in physical disability status was 2.16 times higher among those who were weak at baseline compared to non-weak individuals.[9] Such disabilities will surely impair their quality of life. New studies also focus on muscle quality such as muscle size, fiber type, architecture, aerobic capacity, intermuscular adipose tissue, fibrosis and neuromuscular activation which may also potentially contribute to muscle function related to mortality and physical disability.[7]

Muscle is the main site of glucose metabolism in our body, as up to 80% of glucose uptake occurs in the skeletal muscle. Therefore, loss of muscle mass and low muscle strength may contribute to degenerative metabolic diseases. Muscle weakness is associated with higher fasting insulin levels and a precursor to insulin resistance, thus, increasing the odds of diabetes.10 This also explains why a diabetic patient needs to include not only endurance exercise, but also resistance/strength training as a part of the disease management. A study involving 424 mid-life women in Michigan found that handgrip strength was independently associated with incidence of diabetes across 16 years of follow up. Each 0.1 higher handgrip strength was associated with a 19% lower hazard of incident diabetes.[10] Another study combining NHANES data from U.S. and CHARLS data from China with a total number of more than 10,000 middle-age and older individuals concluded that handgrip strength was robustly associated with cardiometabolic disease risk and physical disability in the U.S. and China aging adults.[11]

Since we already know the detrimental effects of low muscle mass and weak muscle strength as we age, we need to implement strategies to prepare ourselves for this phenomenon since aging is inevitable. A study showed that doing lifelong aerobic exercise gives substantial benefit in our cardiopulmonary capacity and preserves capillarization and aerobic enzymes in our skeletal muscle. Therefore, skeletal muscle fitness may be easier to maintain with lifelong exercise.[12] It is also recommended that resistance exercise, which can attenuate or reverse the age-associated disabilities and decrease in muscle strength and mass, is a fundamental component of the treatment program in both men and women.[6,7] Strength training should also be used to prevent or treat people with cardiometabolic disease, thus protecting against premature mortality.[8,10] Then, the final question is, when do we need to start? The answer is as simple as "as soon as possible." American College of Sports Medicine recommends multi-joint strength exercises that target all major muscle minimum two days a week.[13] So, it's never too late to incorporate strength training into our exercise program. Muscle mass and muscle strength is not something we can build overnight. Strength training takes time, dedication, and effort to see the results and effects, so we have to be patient. Start now while we are younger, or we'll regret it when we are older.

REFERENCES

1. Santana FM De, Domiciano DS, Gonçalves MA, Machado LG, Figueiredo CP, Lopes JB, et al. Association of Appendicular Lean Mass , and Subcutaneous and Visceral Adipose Tissue With Mortality in Older Brazilians : The São Paulo Ageing & Health Study. J Bone Miner Res. 2019;34(7):1264–74.

2. WHO. Global Health Observatory (GHO) Data : Life expectancy [Internet]. 2016. Available from: https://www.who.int/gho/mortality_burden_disease/life_tables/situation_trends_text/en/

3. Bhaskaran K, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality : a population-based cohort study of 3 · 6 million adults in the UK. LANCET Diabetes Endocrinol [Internet]. 2018;6(12):944–53. Available from: http://dx.doi.org/10.1016/S2213-8587(18)30288-2

4. Deutz NEP, Ashurst I, Ballesteros MD, Bear DE, Cruz-jentoft AJ, Genton L, et al. The Underappreciated Role of Low Muscle Mass in the Management of Malnutrition. J Am Med Dir Assoc [Internet]. 2019;20(1):22–7. Available from: https://doi.org/10.1016/j.jamda.2018.11.021

5. Srikanthan P, Karlamangala AS. Muscle Mass Index as a Predictor of Longevity in Older-Adults. Am J Med. 2014;127(6):547–53.

6. Janssen IAN, Heymsfield SB, Wang ZIM, Ross R, Heymsfield SB, Wang Z. Skeletal muscle mass and distribution in 468 men and women aged 18 – 88 yr. J Appl Physiol. 2000;89:81–8.

7. Mcgregor RA, Cameron-smith D, Poppitt SD. It is not just muscle mass : a review of muscle quality , composition and metabolism during ageing as determinants of muscle function and mobility in later life. Longev Heal. 2014;3(9):1–8.

8. Duchowny K, Arbor A. Do Nationally Representative Cut-points for Clinical Muscle Weakness Predict Mortality ? Results From 9 Years of Follow-up in the Health and Retirement Study. J Gerontol A Biol Sci Med Sci. 2019;74(7):1070–5.

9. Duchowny KA, Clarke PJ, Peterson MD. Muscle Weakness and Physical Disability in Older Americans: Longitudinal Findings from the U.S. Health and Retirement Study. J Nutr Heal Aging. 2018;22(4):501–7.

10. Karvonen-Gutierrez CA, Peng Q, Peterson M, Duhowny K, Nan B, Harlow S. Low grip strength predicts incident diabetes among mid-life women : the Michigan Study of Women ' s Health Across the Nation. Age Ageing. 2018;47(May):685–91.

11. Peterson MD, Chen X, Zhao Y. Low Normalized Grip Strength is a Biomarker for Cardiometabolic Disease and Physical Disabilities Among U . S . and Chinese Adults Editor ' s Choice. J Gerontol A Biol Sci Med Sci. 2017;72(11):1525–31.

12. Gries AKJ, Raue U, Perkins RK, Lavin KM, Brittany S, Trappe TA, et al. Cardiovascular and Skeletal Muscle Health with Lifelong Exercise. J Appl Physiol. 2018;125(5):1636–45.

13. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 9th edition. Lippincott Williams & Wilkins; 2014.

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