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Antibiotic usage at a private hospital in Central Java: results of implementing the Indonesian Regulation on the Prospective Antimicrobial System (Regulasi Antimikroba Sistem Prospektif Indonesia [RASPRO])

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Abstract

Methods: A pre–post-descriptive study was conducted in 2019 for 3 months at a private hospital in Central Java, Indonesia, to evaluate the implementation of the Regulation on Indonesian Antimicrobial Stewardship Program (ASP), namely, the Prospective Antimicrobial System/Regulasi Antimikroba Sistem Prospektif Indonesia (RASPRO). Outcomes were measured before and after the implementation of the RASPRO in the ward including: 1) intravenous antibiotic defined daily dose (DDD) per 100 patient-days, 2) antibiotic expenditure, and 3) antibiotic expenditure per inpatient.

Result: The total antibiotic consumption was expressed in DDD/100 patient-days. For the levofloxacin category, the number increased intensely from 2.38 to 15.29; carbapenem escalated from 0.51 to 2.31, ceftriaxone from 32.10 to 38.03, and ampicillin sulbactam from 1.14 to 1.18. In contrast, cefuroxime significantly reduced from 17.25 to 1.38, cefotaxime decreased from 10.33 to 6.83, gentamicin decreased from 3.18 to 1.91, and amikacin decreased from 2.27 to 2.13. The overall cephalosporin usage decreased from 19.89 to 15.41. The total antibiotic expenditure had a decline of 20.28%, followed by 14.44% reduction on the percentage of antibiotic expenditure per inpatient.

Conclusion: Our study describes the 3-month analysis of antimicrobial usage before and after the implementation of the RASPRO by evaluating several parameters. The antibiotic consumption expressed in DDD/100 patient-days for each antibiotic category has demonstrated that there are different impacts that may be debatable and calls for further evaluation. A decrease in the total antibiotic expenditure has also been reported. However, since our study is a preliminary study, it should be continued by further studies that involve longer study duration to observe further impacts of the program.

Keywords: anti-bacterial agents; antimicrobial stewardship; antimicrobial drug resistance; Indonesia

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uch attention is currently given to the global health situation, particularly on global medical regulation emphasizing the prudent use of antibiotics. For this purpose, the Antimicrobial Stewardship Program (ASP) has been proposed worldwide to address the problems of antimicrobial resistance (AMR) and to optimize empiric antibiotic treatment; however, its implementation has unexpectedly faced some serious obstacles. Our study group has developed regulations and a system to implement the ASP, known as the Indonesian Regulation on the Prospective Antimicrobial System (Regulasi Antimikroba Sistem Prospektif Indonesia [RASPRO]). The RASPRO was introduced at a

private hospital in Central Java, Indonesia, in 2019. The development of RASPRO was inspired by the Selective Pressure Theory and Risk Stratification for Antimicrobial Resistance, and it was mutually agreed by all members of the hospital peer group to carry out the program.

Background

Many influencing factors may distance clinicians from the prudent use of antibiotics. In resource-poor settings, there is a complex social reality that may affect a clinician's antibiotic prescribing behavior, including patient socioeconomic class, patient demand for antibiotics, competition among practitioners, and conflict of interest arising from the physician's social relationship with his/her patient (1). Ben Ami et al. demonstrated that 34.5% bacterial isolates of community patients produced extended-spectrum beta-lactamases (ESBLs), which might also affect the use of antibiotics along with a number of other risk factors such as recent antibiotic treatment, recent hospitalization, and geriatric (>65 years old) and male patients (2). Drynka et al. suggested that other factors may include a history of multi-drug resistance (MDR) colonization; moreover, multi co-morbidities also have their own rules for developing the risk of MDR infection (3).

Falagas et al. mentioned that specific microorganisms accounted for MDR such as ESBL-producing microorganisms, methicillin-resistant Staphylococcus aureus (MRSA), and carbapenemase producers. These microorganisms may cause serious problems and should be controlled immediately, particularly the ESBL-producing microorganisms that are frequently observed as a major problem in both community and hospital settings. Meanwhile, Acinetobacter baumannii and Pseudomonas aeruginosa isolates showed a high resistance to antibiotics in hospital settings (4, 5). Between 2007 and 2008, a study conducted at three teaching hospitals in Indonesia revealed that 24% patients who had undergone surgical procedures were screened positive for S. aureus at the time of hospital discharge and 4.3% of them were with MRSA carriage (6). In 2003, Hadi et al. suggested that the proportion of antibiotic misuse in Indonesia reached 84% (7). The antibiotics were inappropriately prescribed without proper indication. Furthermore, another study in 2012 demonstrated a reduced number of misused antibiotic treatment and lower prevalence of ESBL infections, particularly those caused by Klebsiella pneumoniae (58%) and Escherichia coli (52%) (7).

Advanced consequences of MDR when antibiotics are customized in daily practice have been clarified by the selective pressure theory (8). Moreover, in 2017, the European Centre for Disease Prevention and Control (ECDC) announced that penicillins and cephalosporins are the most commonly prescribed antibiotics (9). Experts in Indonesia have aspired to detract from unnecessary antibiotic prescription and therefore seek to share their ideas on how to implement an ASP for their country. Considering the fact that most antibiotics are prescribed as empiric treatment, the Ministry of Health (MoH) of the Republic of Indonesia has stipulated regulations that suggest reduced antibiotic consumption expressed in defined daily dose (DDD) per 100 patient-days and antibiotic expenditure are good indicators of a successful ASP. The regulations also emphasize that those parameters must be well documented as they may be associated with the cost-effectiveness of antibiotic treatment in daily practice. The RASPRO was developed as a consensus for implementing the MoH regulations as well as to provide

clinician guidelines on the prudent use of antibiotics in daily practice.

Methods

By considering the previous antibiotic consumption and history of hospital admission within the last 90 and 30 days, the risk assessment for potential multidrug-resistant pathogens using the Assessment of Risk of MDR pathogens in Community-onset Pneumonia (ARUC) Score can empirically predict the probability of MDR-bacterial infection in patients with pneumonia (10). There are also other factors for predicting the probability of MDRinfection pneumonia, as calculated by Aliberti et al. who included both the history of antibiotic treatment and hospitalization within the last 90 days with any other factors such as immunocompromised health status and concomitant disease of chronic pulmonary disease (11). Moreover, Gomila et al. have apprised various risk factors accounting for MDR infection among hospitalized patients with complicated urinary tract infection. These factors are history of previous urinary tract infection within the last 1 year period, history of hospitalization, invasive treatment, and previous antibiotic consumption within the last 30 days (12). To predict the probability of getting ESBL Enterobacteriaceae infection, Tumbarelo and Duke have considered many other factors including the Charlson co-morbidity, antibiotic consumption, the use of immunosuppressant treatment within the last 90 days, and any installation of medical instrument within the last 30 days (13). Considering all the above-mentioned risk factors for their patients, clinicians should be provided with a guideline on when to use a narrow-spectrum, anti-ESBL antibiotics, or a broad-spectrum (anti-Pseudomonas, anti-Acinetobacter spp.) antibiotics for empirical treatment.

Taking all these factors into account, we strived to develop a tool that may serve as a system for clinicians to provide appropriate antibiotic prescription. The RASPRO is a consensus that has been developed for hospital settings, and the system is established based on a number of studies and literature references to facilitate the antimicrobial stewardship implementation in Indonesia. Both community-acquired infections (CAIs) and healthcare-associated infections (HAIs) are covered in the RASPRO with various possibilities of multi-sensitive, ESBL or MDR infection by considering the severity of the infection, host characteristics, immune status, previous antibiotics use, history of hospitalization, and installed medical instrument.

The RASPRO was also established at a private hospital in Central Java, Indonesia. The establishment of RASPRO was then followed by the quantification of the impact of antibiotic use adopting the DDD method, expressed in DDD/100 patient-days as well as the quantification of antibiotic expenditure within the 3-month period before and after the implementation of the RASPRO. While performing the evaluation, we also expect that reduced antibiotic usage may improve the indicators of antimicrobial stewardship implementation consistent with those outlined by the regulation of the MoH of the Republic of Indonesia. As mentioned above, the RASPRO is a consensus for implementing the ASP in Indonesia, which consists of two flowcharts and two forms. The first flowchart is RASAL (RASPRO Alur Antibiotik Awal) or the First Flowchart of Antibiotic Use (Figure 1), and the second flowchart is RASLAN (RASPRO Alur Antibiotik Lanjutan) or the

NO.	SPECIFICATION	FLOW	STOP	TREATMENT A	в
1.	Bacterial infection site(s) & symptoms clearly explained	No	STOP	No AB Treatment	
		Yes	Site(s):		
2.	Sepsis/Febrile Neutropenia/Categorized into HAIs	Yes	STOP	Stratification Type III	
		No			
3.	Organ perforation	Yes	STOP	Stratification Type III	
		No			
4.	Bacterial infection encephalopathy	Yes	STOP	Stratification Type III	
		No			
5.	Immunocompromised and/or uncontrolled DM with history of antibiotic(s) taking in the last 30 days	Yes	STOP	Stratification Type III	
		No			
6.	Immunocompromised and/or uncontrolled DM with history of hospitalization more than 48 hours in the last 30 days	Yes	STOP	Stratification Type III	
		No			
7.	Immunocompromised and/or uncontrolled DM with history of medical devices usage in the last 30 days	Yes	STOP	Stratification Type III	
		No			
8.	Immunocompromised and/or uncontrolled DM with history of antibiotic(s) taking in the last 90 days	Yes	STOP	Stratification Type II	
		No			
9.	Immunocompromised and/or uncontrolled DM with history of hospitalization more than 48 hours in the last 90 days	Yes	STOP	Stratification Type II	
		No			
10.	Immunocompromised and/or uncontrolled DM with history of medical devices usage in the last 90 days	Yes	STOP	Stratification Type II	
		No		Stratification Type I	

AB = Antibiotic

HAIs = Healthcare Associated Infections

DM = Diabetes Mellitus

Fig. 1. RASAL flowchart.

Flowchart of Advanced Antibiotic Use (Figure 2). Furthermore, as shown in Figure 3, the first form of RASPRO is for prolonged antibiotic use or RASPRO Formulir Antibiotik Berkepanjangan (RASPRAJA), and the second form, as shown in Figure 4, is the form for culture-based antibiotic treatment, which is known as RASPRO Formulir Antibiotik sesuai kultur (RASPATUR).

The RASAL flowchart is used for the first assessment in the inpatient setting, which is considered as the first administration of antibiotic treatment. The flowchart should be filled by clinicians when prescribing the first antibiotic treatment for their hospitalized patients. However, it should be noted that the flowchart is not a diagnostic tool, but serves as a consensus as it is based solely on literature reviews. Furthermore, it should also be considered that the flowchart is modified from the Carmeli's Score of Risk Stratification containing three types of risk stratification (14, 15). The Carmeli Score-like criteria in the flowchart are developed to provide risk stratification for infections that are complicated by multi-sensitive, ESBL-producing and other MDR microorganisms.

Similar to the Carmeli Score, the RASAL consists of three types of stratification, but it has an additional highlight, that is, severity of infection, which is one of the important aspects that must be carefully considered when administering antibiotic treatment. Nevertheless, the flowchart includes the term 'patient's stratification' instead of 'risk stratification'. Stratification type 1 is used for inpatients in need of narrow-spectrum antibiotic treatment; the stratification type 2 is reserved for those who need empiric anti-ESBL treatment; stratification type 3 is utilized to justify the use of empiric broad-spectrum antibiotic treatment.

The RASAL flowchart is utilized only during the first antibiotic prescription for inpatients. The site of infection should be clearly declared by clinicians based on their impression of clinical manifestations and any other findings.

NO.	SPECIFICATION	FLOW	STOP	TREATMENT	FIRST AB	ADVANCE AB
1.	Clinical symptom(s) of infection still present	No	Stop	De-escalation due to the culture result/AB step-down to the lower stratification/switch from IV to oral/AB stop		
		Yes	Site	e(s):		
2.	Sepsis/Febrile Neutropenia/ Categorized into HAIs	Yes	Stop	Antibiotic escalation to stratification type 3		
		No				
3.	Organ perforation	Yes	Stop	Antibiotic escalation to stratification type 3		
		No				
4.	Bacterial infection encephalopathy	Yes	Stop	Antibiotic escalation to stratification type 3		
		No				
5.	Clinical symptom(s) improved between 3 to 7 days antibiotic treatment	No	Stop	AB escalation to the next stratification/AB added due to the guidelines		
		Yes	step-down	ion due to the culture result/AB to the lower stratification/switch rom IV to oral/AB stop		

AB = Antibiotic

IV = Intravenous

HAIs = Healthcare Associated Infections

Fig. 2. RASLAN flowchart.



Fig. 3. RASPRAJA form.

Clinicians must fill out the form by answering all the closedtype questions from top to bottom by circling YES or NO. When the answer (either YES or NO) parallels with the word STOP, then the patient will be categorized into a type of stratification. The flowchart subsequently provides a guideline to clinicians on when to use the narrow-spectrum antibiotic treatment (stratification type 1), anti-ESBLs treatment (stratification type 2), or empiric broad-spectrum antibiotic treatment (stratification type 3). The antibiotic provided for each stratification is based on our local guidelines so that clinicians can provide empiric treatment.

There is a restriction rule for clinical pharmacists to decline antibiotic dispensing. Antibiotics should not be dispensed when the site of infection is not clearly declared in the flowchart or when the antibiotic prescription is not consistent with the hospital antibiotic guidelines.

In the case of altered antibiotic regimens, which should be consistent with the patient's clinical condition, RASLAN or the RASPRO second flowchart can be used. The flowchart should be filled out completely by clinicians when there is a need to change the antibiotic regimen as necessary, either for antibiotic escalation or de-escalation while awaiting culture results.

Similar to the RASAL flowchart, it should also be filled out in a top-down fashion whenever empiric antibiotics treatment should be stepped down, escalated, replaced, or added for combination regimens. When the answer YES or NO parallels with the word STOP, clinicians should confirm the instruction in the TREATMENT column, fill in the blank about the first antibiotic treatment that has been used, and the altered or advanced antibiotic treatment (stepped down, escalated, replaced, or added). Restriction on antibiotic dispensing should be enforced by clinical pharmacists when the antibiotic step down, escalation, replacement, or addition is not consistent with the hospital antibiotic guidelines.

The antibiotic sensitivity pattern of local microorganisms in Indonesia was issued by the Indonesian Society of



Fig. 4. RASPATUR form.

Clinical Pathologists in 2018, and it became the basic data for developing the hospital antibiotic guidelines. The pattern was obtained from 31 hospitals across the country since Indonesia has no accumulative national data. The pattern showed that the most common infecting gramnegative bacteria were Klebsiella pneumonia, Escherichia coli, and Pseudomonas aeruginosa; the majority of gram-positive infecting bacteria were Staphylococcus aureus and Enterococcus faecalis. Most microorganisms showed middle to low rate of sensitivity to ceftriaxone and quinolones, while P. aeruginosa showed middle to high rate of sensitivity to aminoglycosides and carbapenems. No definitive data were available for the local ESBL-producing microorganisms. However, the Internal Antimicrobial Stewardship Committee (IASC) has approved the use of ampicillin sulbactam as anti-ESBL antibiotic regimen for the hospital setting.

Considering all data findings, the IASC concluded that levofloxacin should be classified as the main antibiotic treatment used for stratification type 1, followed by ceftriaxone and other cephalosporins. Furthermore, ampicillin sulbactam is the antibiotic class used for stratification type 2, while carbapenems are the main antibiotic treatment for stratification type 3, followed by amikacin and gentamicin. The committee does not include tazobactam piperacillin in the guideline as treatment for eradicating ESBL-producing microorganisms since hospital supply of the antibiotic was not available.

As mentioned earlier, the RASPRO system has two forms. The first is the RASPRAJA, which should be filled out by clinicians when prescribing antibiotic treatment for more than 7 days. The clinicians should also fill out the form to convince the IASC that such prolonged use of antibiotic treatment is appropriate and necessary for eradicating persistent infection.

The last form of RASPRO is RASPATUR. RASPATUR should be completed by clinicians when they prescribe the culture-based antibiotic treatment.

The IASC issued the Hospital Antibiotic Guidelines with recommendations of empirical antibiotic treatment available for each type of stratification. We did some internal supervision followed by several 3-month analyses before and after the implementation of the RASPRO. Our data were secondary data, and they were processed by the RASPRO Indonesia Study Group and had been approved by the IASC. Data used in this study are secondary data, processed by the RASPRO Indonesia Study Group, and approved by the IASC.

MoH-based parameters were evaluated for 3 months before and after the implementation of the RASPRO in mid-2019. We documented and performed follow-up sessions on antibiotic consumption, which was expressed in DDD/100 patient-days and on antibiotic expenditure. Our findings showed that there were a total of 13,231 hospitalized patients within the 3-month period including 6,848 patients and 6,383 patients before and after 3 months of the RASPRO implementation. We compared three aspects between before and after the implementation of the program, which were: 1) intravenous antibiotic DDD/100 patient-days, 2) antibiotic expenditure, and 3) the percentage of antibiotic expenditure per inpatient. The comparison was performed conscientiously. Antibiotic consumption was expressed in DDD/100 patient-days using a calculation formula suggested by the World Health Organization (WHO). We observed all of these aspects, comparing them between before and after the implementation of the RASPRO, and our observation was also monitored by the IASC.

Results

The antibiotic consumption was expressed in DDD/100 patient-days and fluctuated for each antibiotic class (Table 1). Such results may have occurred due to hospital antibiotic guidelines specifying the antibiotics to be used

for each type of infection, with antibiotic usage needing to be strictly consistent with the proposed stratification.

Levofloxacin showed a significant elevation in DDD/100 patient-days average in the 3-month period before and after the implementation of the RASPRO, followed by carbapenem, ceftriaxone, and sulbactam ampicillin, although the increases were not as significant as levofloxacin.

Overall, DDD/100 patient-days for cephalosporins decreased from 19.89 to 15.41 in the 3-month period before and after the implementation of the RASPRO (Table 2).

We found a 20.28% reduction of antibiotic expenditure, and a 14.44% reduction of antibiotic expenditure for inpatient settings in the 3-month period before and after the implementation of the RASPRO (Table 3).

Table 1. The average antibiotic consumption (DDD/100 patient-days) in the 3-month period before and after the implementation of the RASPRO

Year 2019	Defined Daily Dose (DDD) /100 patient days								
	Ampicillin								
	Levofloxacin	Carbapenem	Ceftriaxone	Cefuroxime	Cefotaxime	Sulbactam	Gentamicin	Amikacin	
3 Months Befor	e								
April	1.83	0.44	36.45	16.65	10.33	1.68	2.68	3.87	
May	2.30	0.60	27.06	13.67	9.92	1.10	3.89	1.18	
June	3.00	0.50	32.78	21.42	10.73	0.65	2.98	1.75	
Average	2.38	0.51	32.10	17.25	10.33	1.14	3.18	2.27	
3 Months After									
July	15.34	1.97	38.81	1.50	8.37	1.36	2.50	2.05	
August	16.44	2.46	38.50	2.60	5.42	1.40	1.11	2.68	
September	14.10	2.49	36.77	0.04	6.71	0.77	2.13	1.65	
Average	15.29	2.31	38.03	1.38	6.83	1.18	1.91	2.13	

Table 2. Reduced average monthly cephalosporin consumption (DDD/100 patient-days) in the 3-month period before and after the implementation of the RASPRO

Year	Defined Daily Dose(DDD)/100 patient days						
	Ceftriaxone	Cefuroxime	Cefotaxime	Average			
3 Months Before							
April	36.45	16.65	10.33	21.14			
May	27.06	13.67	9.92	16.88			
June	32.78	21.42	10.73	21.64			
Average	32.10	17.25	10.33	19.89			
3 Months After							
July	38.81	1.50	8.37	16.23			
August	38.50	2.60	5.42	15.51			
September	36.77	0.04	6.71	14.51			
Average	38.03	1.38	6.83	15.41			

Year 2019		Antibiotic	Antibiotic	
	Inpatients	Expenditure	Expenditure/Inpatients	
3 Months Before				
April	2,409	21,730	9.02	
May	2,209	21,156	9.58	
June	2,230	21,913	9.83	
Total	6,848	64,799		
Average	2,283	21,600	9.47	
3 Months After				
July	1,996	17,049	8.54	
August	2,118	16,658	7.86	
September	2,269	17,954	7.91	
Total	6,383	51,661		
Average	2,128	17,220	8.11	
Average % of Decreasing	6.79	20.28	14.44	

Table 3. A comparison of antibiotic expenditure in the 3-month period before and after the implementation of the RASPRO for inpatient settings

Discussion

The significant increase of levofloxacin and carbapenem consumption, expressed in DDD/100 patient-days, is likely to occur since according to the IASC they are the first-line antibiotics for RASPRO stratification type 1 infection and for stratification type 3 infection in the hospital antibiotics guideline.

Ben Ami et al. in 2009 demonstrated that there was an increased prevalence of ESBL-producing bacteria in the community isolates with CTX-M type as the dominant phenotype (2). Such a phenomenon may be associated with the widespread use of cephalosporin as it is the most common antibiotic used in daily practice (9). The recommendation to use levofloxacin as the first-line treatment for stratification type 1 infection may limit the use of beta-lactam antibiotics, and as a result of this guideline, the overall cephalosporin usage expressed in DDD/100 patient-days decreased from 19.89 to 15.41.

The total cephalosporin consumption, including cefuroxime and cefotaxime, expressed in DDD/100 patient-days reduced within 3 months after the implementation of the RASPRO. Nevertheless, an increased use of ceftriaxone was observed from 32.10 to 38.03 DDD/100 patient-days. We think that these data pertain to the fact that ceftriaxone is also recommended as the first alternative treatment following levofloxacin for stratification type 1 infection. A slow increase of ampicillin sulbactam has also been reported.

It has been recently observed that carbapenemase-producing microorganisms have brought a novel threat of antibiotic resistance problems worldwide. In 2005, Pagani et al. began to report an outbreak of carbapenemase producers in a hospital setting (16); Tam et al. described that almost all *Acinetobacter* spp. they found had MDR characteristics and that carbapenemase producers (VIM-2) were among them (17). Only 21% of these isolates were resistant to aminoglycosides (15). In response to these findings, the IASC recommends carbapenem as the main antibiotic for stratification type 3 infection. Aminoglycosides, in combination with carbapenem, is reserved for severe cases of stratification type 3 infection. Our study showed an increase in carbapenem consumption from 0.51 to 2.31 DDD/100 patient-days in the 3-months period before and after the implementation of the RASPRO. However, we also observed reduced consumption of gentamicin from 3.18 to 1.91 DDD/100 patient-days as well as amikacin from 2.27 to 2.13 DDD/100 patient-days.

When we compared the results with previous studies, we found that there is also a significant reduction of broad-spectrum antibiotic consumption including carbapenems and cephalosporins within 3 months before and after the implementation of RASPRO in other private hospitals in Indonesia (18). Furthermore, the study showed reduced antibiotic expenditure up to 75.42, 93.80, and 70.05% of 1 g meropenem, ceftazidime, and cefepime, respectively (18). Another system called a pre-authorization system, mentioned by Chung et al. in their 6-year retrospective multicenter study at three hospitals in Taiwan, suggested that a pre-authorization system may result in a significant escalation of broad-spectrum antibiotics utilization. Nevertheless, some declining trends have also been reported in one hospital when a total pre-authorization system took place as compared to two others that only used a partial pre-authorization system, which did not include the intensive care unit (19).

Within the 3-month period after the RASPRO had been applied, we found reduced total antibiotic expenditure of 20.28% and a 14.144% reduction of antibiotic expenditure per inpatient. It indicates a decrease in antibiotic consumption for the inpatient setting. The association between RASPRO implementation and these findings still could not be fully understood. The ASP aims to minimize unnecessary use of antibiotics and promote appropriate antibiotic prescribing, which may lead to improved patient outcomes, cost-effective therapy, and reduced adverse consequences of antimicrobial use, including AMR (20, 21). Nevertheless, it is sometimes difficult to draw a direct association between the system interventions and their effects. In hospital sectors, many studies on the efficacy of ASP have reported data about structural and process measures, such as the presence of guidelines and reduction in antimicrobial use (20, 21).

Conclusion

This study has described the 3-month analysis of antimicrobial use before and after the implementation of the RASPRO by evaluating several parameters. The antibiotic consumption expressed in DDD/100 patient-days for each antibiotic category has demonstrated that there are different impacts that may be debatable and calls for further evaluation. A decrease in the total antibiotic expenditure has also been reported. However, since our study is a preliminary study, it should be continued by further studies that involve longer study duration to observe further impacts of the program.

Conflict of interest and funding

The authors have declared that they have no conflict of interest regarding this study. The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

Ethics approval

Ethics approval was obtained from the Ethical Committee of Trisakti School of Medicine, Trisakti University, Indonesia, on February 7, 2020. Correspondence no. 155/ KER/FK/II/2020.

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