Original article

A Clinical-Based Drug Interaction Alert (CIDIA) System for Preventing Drug Interaction and Its Associated Factors at Rural Primary Care Centres

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Abstract:

Objectives: Drug-drug interaction (DDI) occurs following the prescription of more than one drug. DDI and its associated factors in Indonesia's country's primary care have not been reported. ***Materials and Methods*:** Through this descriptive cross-sectional study, we analysed the DDI incidence using the Clinical-Based Drug Interaction Alert (CIDIA) alert system. Purposive research was carried out by analysing prescriptions (n=2410) from nine primary health cares. ***Results****:* CIDIA alert system detected 7.5% DDI incidence in all prescriptions, categorized as mild (63%), moderate (36%) and serious (1%). Significant DDI incidence was observed in female patients ($p<0.01$), in patients older than 18 years ($p<0.01$) and in patients receiving three or more drugs ($p<0.01$). The most frequent incidence of DDI from each category was paracetamol-domperidone; dexamethasone-mefenamic acid and captopril-allopurinol. ***Conclusion:*** CIDIA alert system has been shown to provide beneficial support in detecting DDI incidence. Careful consideration should be addressed particularly towards female patients, older patients, and patients receiving three or more drugs in preventing DDI incidence.

Keyword: drug interactions; female; patients; prescriptions; primary health care

Bangladesh Journal of Medical Science Vol. 22 No. 03 July'23 Page : 667-675
DOI: https://doi.org/10.3329/bjms.v22i3.66962

Introduction:

Drug-drug interaction (DDI) is defined as the effects that may appear as a result of interactions between drugs prescribed at the same time. Interactions may appear pharmacodynamically or pharmacokinetically and may be synergistic or antagonistic in their action.[1] Synergistic action is defined as one drug enhancing another drug's activity so that the overall effect is greater than the additive effect, while antagonistic action is defined as one drug impeding or eliminating another drug's activity so that the overall effect is less than the additive.[2] DDI contributes not only to beneficial effects of combined-drugs but also to some harmful effects, in the form of adverse drug reactions (ADRs).[3,4] Thus, the most challenging aspect of DDI is to decide whether the interaction is beneficial or harmful. Notably, only some DDI may lead to harmful effects which result in actual ADR with significant clinical outcomes.[5,6] Nevertheless, the incidence of DDI should be prevented early, even though only a small number of cases may lead to significant ADR with clinical symptoms, given that the complexity of human biological systems and networks may result

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in different DDI responses.[2,5,7,8] Strategies proposed to reduce the risk of DDI including minimizing the number of drugs prescribed, education relating to toxicity and side effects, dose and frequency adjustment and integrating pharmacology in clinical phase of medical students.[9,10] Additionally, developing alert systems using multiple platforms and approaches may also prevent further effects of DDI. These alert systems can automatically remind health workers about potential DDI and directly help them to make final decisions about prescriptions given to patients.[11-19]

Furthermore, these systems also help health workers to decide whether to avoid or accept DDI by changing the drugs prescribed, or to accept the likelihood of interactions and intensively monitor them, or to accept DDI in the case of minor interactions.[11,20]

DDI incidence at the primary care level is rarely reported in Indonesia since most of the DDI alert systems in place are limited to use. Unlike hospitals, most primary health care (PHC) providers do not use an integrated and automatic DDI alert system. They evaluate DDI incidence manually by random checking and remind health workers only after their evaluations are concluded. Considering this current situation, DDI incidence should be strictly monitored in PHCs as well as in hospitals for several reasons. First, most PHCs do not have specific alert systems to automatically detect DDI in chronic and older patients who tend to receive polypharmacy prescribing. Second, primary care patients are not continuously followed up, with the result that patients are not aware of DDI incidence. Third, DDI detection in a particular centre also depends on the literacy of the primary care physician (PCP). Peabody et al., (2018) mentioned in their study that 303 board-certified family and internal medicine practitioners in the US did not recognize or adequately treat DDI and recommended that better methods should be proposed to detect DDI in the primary care setting.[21] Other reports have identified 26% drug interactions at a Bandung drug store,[22] and 59% in chronic patients at a hospital;[23] however, the DDI incidence in Indonesia's primary care system is largely unknown and DDI detection in primary care using automatic alert systems has not been reported. In this study we developed the CIDIA alert system – a drug alert system used by the PHCs – with the aim of gaining better knowledge of DDI and its associated factors in the primary care setting and helping health workers to detect potential DDI. To our knowledge, this is the first study profiling DDI incidence at the PHCs using a drug alert system.

Methods and Materials:

Clinical-Based Drug Interaction Alert (CIDIA) alert system

CIDIA alert system is an application based on several references including textbooks, MIMS, journals and other DDI alert systems for the specific use of DDI detection in primary, secondary or tertiary health care services. As depicted in Figure 1, the CIDIA alert system dashboard includes number of prescriptions, number of daily prescribed drugs, brand name of drugs and number of daily DDIs. Additionally, the CIDIA alert system can detect DDI incidence and categorize DDI as mild, moderate, or serious (Figure 2). The CIDIA alert system was registered in the intellectual property rights of Indonesian Ministry of Law and Human Rights as an alert system with the certificate number EC00201978384.

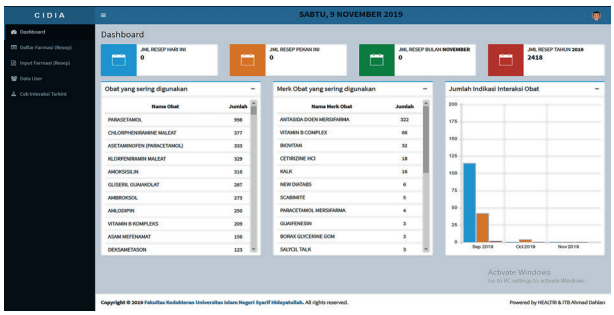

Figure 1. CIDIA alert system dashboard in Indonesian language implemented in PHCs

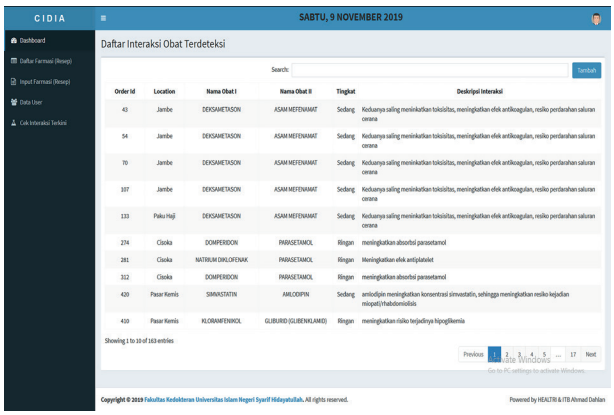

Figure 2. Description of drug interaction category detected by CIDIA in Indonesian language (*Daftar Interaksi Obat Terdeteksi*)

Design of the study

This cross-sectional study included prescriptions registered in the CIDIA alert system provided to

all patients in all age groups who attended nine PHCs in the district of Tangerang, Banten Province: Paku Haji (PH), Cisoka (CS), Pasar Kemis (PK), Tigaraksa (TG), Jambe (JB), Rajeg (RJ), Sukawali (SK), Kedaung Barat (KB) and Pasir Nangka (PN). The prescriptions samples were taken purposively from the CIDIA alert system as total cohort sampling over a 14-day period.

Prescription sampling

All prescriptions from nine PHCs in Tangerang district were consecutively chosen from the CIDIA alert system regardless the patient diagnosis. Prescriptions for parenteral or topical treatments only or children's concoction drugs were excluded from the study.

Statistical analysis

Data were analysed using the CIDIA alert system and shown as descriptive data by number and percentage. Statistical analysis was performed separately using non-parametric chi-squared testing with significance level of $p<0.05$ wherever applicable.

Ethical Approval:

This research proposal was accepted by the Ethics Committee Faculty of Medicine Universitas Islam Negeri Syarif Hidayatullah with the registry number of B-005/F12/KEPK/TL.00/02/2021

Conflict of interest: None declared.

Results:

CIDIA alert system

CIDIA alert system is displayed in the Indonesian language to simplify the process for health workers of inputting all PHC prescription data. As depicted in Figure 1, the dashboard of the CIDIA alert system includes real-time data for most-used generic drugs (*obat yang sering digunakan*), most-used branded drugs (*merk obat yang sering digunakan*), DDI incidences (*jumlah indikasi interaksi obat*), weekly number of prescriptions (*jumlah resep pekan ini*), monthly number of prescriptions (*jumlah resep bulan*), and annual number of prescriptions (*jumlah resep tahun ini*). Furthermore, patients' details including gender, age, disease categorization, type of prescribed drugs and drug interaction category are also included in the CIDIA alert system, as displayed in the Figure 2 as mild (*ringan)*, moderate (*sedang)* and serious (*berat)*.

General characteristics

During the study, 2410 prescriptions were purposively collected from CIDIA alert system. As displayed in Table 1, prescriptions were predominantly issued to patients in the 19 to 59 age group (56%). Smaller percentages were for patients aged 1 to 5 years (18%) and 5 to 18 years (16%). Based on gender, prescriptions were predominated by those provided to female patients (63%), almost twice as many as to male patients (37%). Further analysis of the prescriptions showed that both male and female patients received the same number of drugs per prescription in average (3 vs. 3).

Table 1. Patient characteristics based on age, gender and average number of drugs

Patient characteristics	Prescriptions (n = 2410)	Percentage (%)
Age		
Less than 1 year old	36	1
1 to 5 years old	437	18
5 to 18 years old	391	16
19 to 59 years old	1338	56
More than 59 years old	208	9
Gender		
Male	883	37
Female	1527	63
Average number of drugs per prescription		
Male	3	
Female	3	

Prescription distribution

According to Table 2, the highest number of prescriptions (629) was from the PH PHC, as a centre covering a large area of the district. Smaller percentages of prescriptions came from CS, PK, TG, JB, RJ, SK, KB and PN, at 19%, 15%, 10%, 10%, 6%, 6%, 4% and 4% of the total 2410 prescriptions, respectively. Differences in number of prescriptions among PHCs in the district depended on the population and coverage area of each.

Table 2. Prescription distribution at each PHC in the district (n = 2410)

PHC	Prescriptions	Percentage (%)
PH	629	26
CS	447	19
PK	372	15
TG	246	10
JB	229	10
RJ	142	6
SK	136	6
KB	105	4
PN	104	4
	2410	100

General distribution of DDI incidences

During the study, the CIDIA alert system detected 181

DDI incidences (7.5%) of 2410 prescriptions from nine PHCs. As depicted in Table 3, DDI incidences were automatically categorized by the CIDIA alert system as mild (63%), moderate (36%) or serious (1%).

Table 3. DDI incidence in the district detected by CIDIA based on categorization, type of DDI, gender, age and number of drugs prescribed per prescription (n=181)

DDI incidence	Percentage (%)	p value
Categorization		
Mild	114 (63)	
Moderate	65 (36)	
Serious	2 (1)	
Type of DDI incidence		
Single	178 (98)	
Multiple	3 (2)	
Gender		0.0015
Male	46 (25)	
Female	135 (75)	
Age		0.0001
Up to 18 years old	26 (14)	
Over 18 years old	155 (86)	
Number of drugs prescribed per prescription		0.001
2 drugs without interaction	682 (28)	
2 drugs with interaction	20 (1)	
≥3 drugs without interaction	1292 (54)	
≥3 drugs with interaction	161 (7)	

Most of the incidences (98%) were single DDIs (between two drugs). However, multiple DDIs were observed in three prescriptions (2%), one prescription with two moderate DDIs, one prescription with two mild DDIs and one prescription with a combination of mild and moderate DDIs (Table 3).

The highest DDI incidence was observed at CS PHC, with 32.6% of the 181 cases (Table 4), detailed as being 24.3% of the total mild cases, 7.7% of total moderate cases and 0.6% of total serious cases (Figure 3).

CIDIA alert system showed that the lowest DDI incidence was observed at PN PHC with 1.7% of 181 cases (Table 4), detailed as being mild cases only (Figure 3). The remaining proportion of total DDI incidence by centre were 24.9%, 9.9%, 9.4%, 8.3%, 6.6%, 4.4% and 2.2% in PK, JB, PH, TG, RJ, KB and SK PHCs, respectively (Table 4). Mild and moderate interactions predominated the categorization of DDI incidence at the nine PHCs; however, different patterns of DDI incidence appeared at each PHC.

Table 4. DDI incidence for each PHC

PHC	DDI incidence (n=181)	PHC incidence compared to total DDI incidence (%)	PHC incidence compared to total PHC prescriptions (%)
PH	17	9.4	3
CS	59	32.6	13
PK	45	24.9	12
TG	15	8.3	6
JB	18	9.9	8
RJ	12	6.6	8
SK	4	2.2	3
KB	8	4.4	8
PN	3	1.7	3

Briefly, mild DDI incidents predominantly appeared in PH, CS, PK, TG, RJ, and PN PHCs. Moderate DDI incidences were predominantly observed in JB and KB PHCs. Only SK PHC had the same proportion of mild and moderate DDI incidences (Figure 3).

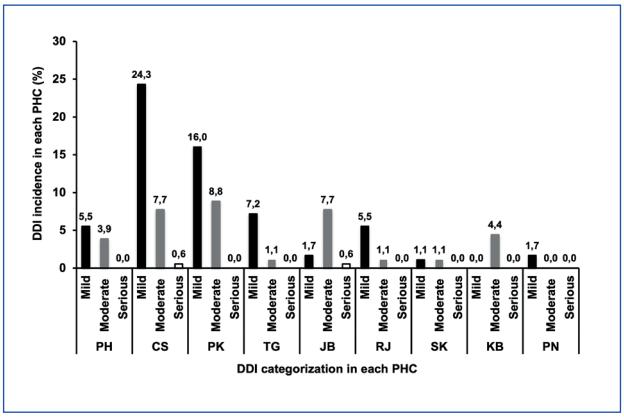

Figure 3. DDI incidence in each PHC (n=181). Black represents mild DDI, grey moderate DDI, and white serious DDI.

Only two PHCs reported serious DDI incidence, these being CS (1 case) and JB (1 case). In conclusion, each PHC had its own pattern of DDI incidence, depending on the literacy and knowledge of its medical workers.

Factors contributing to DDI incidence

Further analysis shows that particular factors contributed to the incidence of DDI, including gender, age and number of drugs prescribed in one prescription. CIDIA alert system showed that prescriptions to female patient predominated at all nine PHCs (1527 females vs 883 males).

Consistent with this distribution, DDI incidences were largely found in prescriptions to female patients (135 cases) compared to male patients (46 cases). In brief, the incidence of DDI in the female patients was significantly greater than male patients (p=0.0015),

even though both female and male patients received the same number of drugs per prescription in average (Tables 1 and 3). Subsequently, we observed that most of the DDI incidences were categorized as mild and moderate for prescriptions to both female and male patients (Table 5) and there were no significant differences of DDI categorization between female and male patients (p = 0.094).

Table 5. DDI incidence categorization based on gender (n=181)

DDI incidence	Percentage (%)	p value
Male		
Mild	23 (13)	
Moderate	22 (12)	
Serious	1 (1)	0.094
Female		
Mild	91 (50)	
Moderate	43 (24)	
Serious	1 (1)	

Additionally, significant DDI incidences were reported in prescriptions to patients older than 18 years (155 cases) compared to younger patients (26 cases) and the difference reached statistical significance at p=0.0001 (Table 3). Further analysis revealed that number of drugs prescribed per prescription also contributed to the incidence of DDI. As depicted in Table 3, DDI incidence was 1% when patients received two drugs in one prescription but increased to 7% when patients received three or more drugs in one prescription (p = 0.0001), suggesting a higher risk of DDI when greater numbers of drugs are prescribed in one prescription.

Most common DDI

Life-saving and low-toxicity drugs are prioritized by primary care centres, while more sophisticated and more toxic drugs and those with limited supply are allocated to tertiary healthcare centres under the overview of more highly trained experts. Therefore, only a limited range of drugs can be used in PHCs for the primary management of patients, with the aim of overcoming primary diseases in their early stages. As displayed in Table 6, the most common incidence of mild DDI in the PHCs studied was between domperidone and paracetamol, in which domperidone can increase the absorption of paracetamol. The most common moderate incidence of DDI was between dexamethasone and mefenamic acid, in which both drugs can increase each other's toxicity through pharmacodynamic synergism. This is followed by amlodipine and simvastatin, in which amlodipine can increase simvastatin concentration; mefenamic acid and captopril, in which mefenamic acid can decrease captopril concentration; mefenamic acid and glyburide, in which mefenamic acid can increase the concentration of glyburide in the plasma; and calcium carbonate and captopril, in which calcium carbonate can decrease captopril bioavailability (Table 6). The only serious DDI incidents observed were between captopril and allopurinol, in which both drugs increase each other's toxicity through pharmacodynamic synergism.

Discussion:

The salient findings of our study were: (1) there were no automatic alert systems integrated into the reporting systems of the PHCs so that a drug alert application system would be required to improve the safety of services; (2) CIDIA alert system found 181 (7.5%) DDI incidence of 2410 prescriptions from nine PHCs and these were categorized as mild (63%), moderate (36%) and serious (1%); (3) significant incidence of DDI was observed in prescriptions to female patients ($p<0.01$), patients older than 18 years ($p<0.01$), and patients receiving three or more drugs ($p<0.01$); (4) the most frequent mild and moderate incidences of DDI were between paracetamol and domperidone and dexamethasone and mefenamic acid, respectively. The most common serious interaction was between captopril and allopurinol.

Using technology for better data analysis will give beneficial support in solving health problem. For example, bioinformatics has been reported to support parasites identification by in silico approach.[24] Big data approach will also play beneficial support in detecting DDI. DDI is defined as effects that may occur from the interaction of drugs prescribed at the same time. Such interactions can have beneficial effects resulting from combined drugs but can also result in ADRs, and so deciding whether a DDI is beneficial or harmful is an important aspect of drug prescribing.[3] DDIs commonly appear in the primary care setting, but only some of them are likely to lead to harmful ADRs with significant clinical outcomes.[5] The incidence of harmful ADR resulting from DDIs should be prevented early in a patient's treatment.[5-8]

In this study, CIDIA alert system detected DDI incidence of 7.5% of 2410 prescriptions from the nine PHCs in the primary care setting.

Additionally, it also detected that these DDI incidences were dominated by those of mild and moderate categorization (99%), though each PHC had its own pattern of DDI categories.

Table 6. Categorization of DDI incidence detected by CIDIA

Categorization	Drug 1	Drug 2	Interaction
Mild	Domperidone	Paracetamol	Domperidone increases the absorption of paracetamol
	Sodium diclofenac	Paracetamol	Paracetamol increases the anti-platelet effect of sodium diclofenac
	Omeprazole	Glyburide	Omeprazole increases the effect of glyburide
	Metformin	Hydrochlorothiazide	Hydrochlorothiazide decreases the effect of metformin
	Magnesium hydroxide	Paracetamol	Magnesium hydroxide increases the absorption of paracetamol
Moderate	Dexamethasone	Mefenamic acid	Both drugs increase toxicity of each other through pharmacodynamic synergism
	Amlodipine	Simvastatin	Amlodipine increases simvastatin concentration
	Mefenamic acid	Captopril	Mefenamic acid decreases captopril concentration
	Mefenamic acid	Glyburide	Mefenamic acid increases the concentration of glyburide in the plasma
	Calcium carbonate	Captopril	Calcium carbonate decreases captopril bioavailability
Serious	Captopril	Allopurinol	Both drugs increase toxicity in each other through pharmacodynamic synergism

Using CIDIA alert system, we concluded that our result was almost the same as those identified in other research, such as 10.8% DDI incidence in 336,295 patients from 206 primary care facilities in Sweden[25] and 12% of 300,000 patients from Blumenau, Brazil.[26] However, higher incidence of DDI was reported from a primary care centre in Zaragoza, Spain, at around 67.6%,[27] in Turkey, at around 33%,[28] in Italy, at around 30.2%,[4] and in Bahia, Brazil, at around 48.9%.[29] Conversely, lower DDI incidences were reported from primary care settings in Brazil, at around 4.9%,[30] and in Malaysia at around 1.6%.[31] Differences in DDI incidence may reflect different populations, different approaches, applications or algorithms used to detect DDI incidence, different categorizations, and different literacy levels in reporting DDI incidence. Previously, it has been reported that 303 certified PCPs did not recognize and adequately treat DDI,[21] indicating that automatic approach should be proposed to detect DDI in primary care services. A better method was already proposed for detecting DDI at primary care centres by developing alert systems that can directly remind health workers of potential DDI.[11-19] In conclusion, CIDIA alert system could detect DDI incidence at the PHCs and along with previous proposed alert system could help PHCs in early detection of potential DDI.

Subsequently, CIDIA alert system have shown that gender is significantly associated with DDI incidence, even though both females and males received the same number of drugs on average. These results are consistent with previous findings.[26-29,31] Female patients have more concerns regarding their health so they tend to visit health centres more than male patients.[32] They also easily recognize symptoms, experience more health problems, and perceive more symptoms than male patients.[32] Furthermore, DDI incidence was significantly found to be almost three times higher for prescriptions to female patients compared to male patients, suggesting a higher risk of ADR in female patients than in male patients.

The statistical null model in one study demonstrated that female-related DDI incidence reflected unknown social or biological causes.[26] The proposed hypothesis of unknown biological or social cause was that female patients received more specific drugs that were more dangerous related to their gender, and/or that health workers did not give appropriate attention to DDI incidence in females.[26,28] Therefore, removing gender-specific drugs such as specific hormonal drugs, could reduce female-related DDI incidence to 4%.[26] Conclusively, using CIDIA alert system, health workers can automatically detect appropriate caution when prescribe drugs to female patients, especially in respect to gender-specific drugs. They can be aware of DDI incidence and fully protect female patients from further ADRs.[26,28] CIDIA alert system also found higher DDI in older patients. The most important explanation of this result is that older people tend to receive polypharmacy due to the complexity of their diseases and this has been reported to play a significant role in the incidence of DDI.[26,28,31,32] Therefore, attention should be addressed to prescribing to elderly patients with the aim of diminishing DDI incidence by periodical reviews of their medicine, reduction in polypharmacy, and preference for monotherapy treatments.[9,32]

We have shown that DDI incidence appeared in 1% of 2410 prescriptions that prescribed two drugs;

however, significant incidence of DDI was observed in greater combinations of drugs. In brief, DDI incidence was significantly increased by around seven times (7% of 2410) in prescriptions for three or more drugs. One study had reported that DDI incidence was 9.8% for prescriptions of two drugs and significantly increased to 88.3% in prescriptions of eight or more drugs.[28] Therefore, our result is consistent with previous findings that DDI incidence appeared to be concomitant with multiple use of drugs.[26,28,31,32] In conclusion, our study validates the view that continuous, integrated and automatic detection of DDI through the implementation of CIDIA alert system in the primary care setting can be an important tool for detecting DDI and thus preventing harmful ADRs associated with it. We also have revealed that at least three factors were found to be significantly associated with DDI incidence, including gender, older age and number of drugs prescribed. Therefore, CIDIA alert system may be beneficial in preventing DDI incidence by giving an alert system for PCPs and health workers in primary care to pay particular attention to female patients, older patients and patients receive three or more drugs.

Finally, using the CIDIA alert system, we can also identify the most common interactions. We have shown that the most common mild DDI incidence in the PHCs studied included sodium diclofenac and paracetamol then omeprazole and glyburide (glibenclamide). Even though the exact mechanism has yet to be conclusively identified, paracetamol has been reported to work synergistically with diclofenac by increasing its anti-platelet activities and thus increasing the risk of post-operative bleeding.[33] Moreover, propacetamol together with sodium diclofenac significantly inhibited platelet aggregation for three times longer than in sodium diclofenac alone in volunteer patients.[34] Furthermore, omeprazole has been reported not only to enhance the hypoglycaemic activity of glibenclamide in animal studies but also to increase its duration and peak effect.[35] Interestingly, pre-treatment with esomeprazole, a drug in the same proton-pump inhibitor class, did not alter the hypoglycaemic activity of glibenclamide, only having effect on hypoglycaemic activity when given at eight times the normal dose.[36] Therefore, in the context of the prevention of hypoglycaemic side effects, a concomitant treatment between glibenclamide and omeprazole should be carefully adjusted, but no further adjustments are needed when glibenclamide and esomeprazole are prescribed together. Additionally, the synergistic effect of omeprazole with glimepiride, a drug with the same class as glibenclamide, has been proposed in diabetic patients for its beneficial interaction effect on glycaemic control.[37]

Conclusion

Strategies for reducing the risk of DDI are not only achieved by re-evaluating therapy on a regular basis, considering non-pharmacologic options, monitoring for signs and symptoms of toxicity or effectiveness, adjusting dosages of medications when indicated, but also by detecting of DDI through an alert system. Through this research, we have shown that CIDIA alert system may help health workers at the PHCs at least in part by detecting potential DDI, categorizing type of interaction and identifying factors associated with DDI incidences.

Acknowledgement:

This work is supported by Pusat Penelitian dan Penerbitan (PUSLITPEN) Universitas Islam Negeri Syarif Hidayatullah Jakarta.

Author's Contributions:

Data gathering and idea owner of this study: FRS, SA

Study design: FRS, SA

Data gathering: FRS, SA, R, MF, FE

Data analysis and consultation: FRS, SA, R, MF, FE

Writing and submitting manuscript: FRS, SA, R, MF, FE

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