COVER

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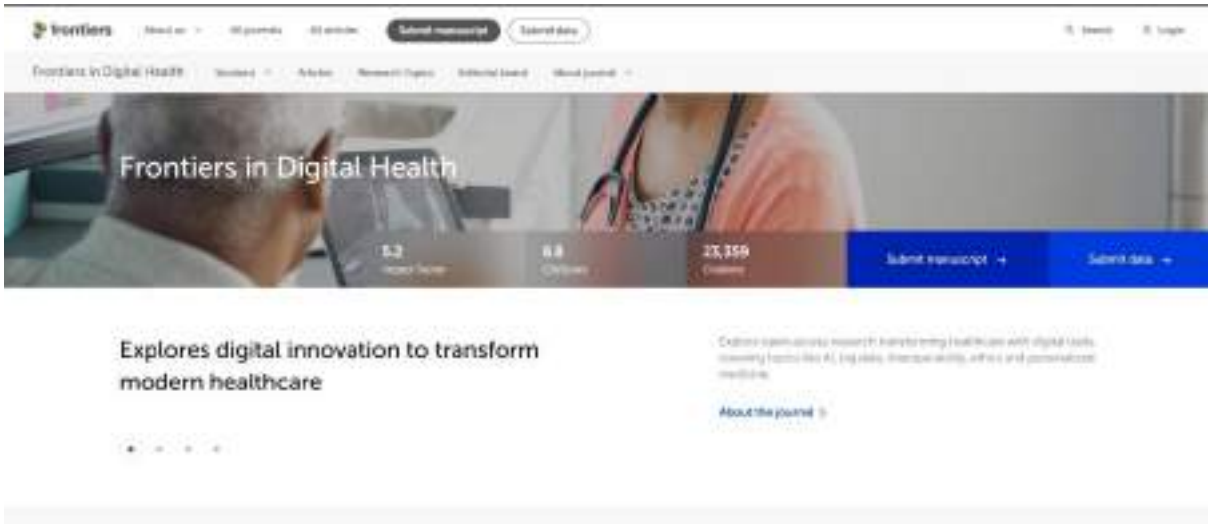

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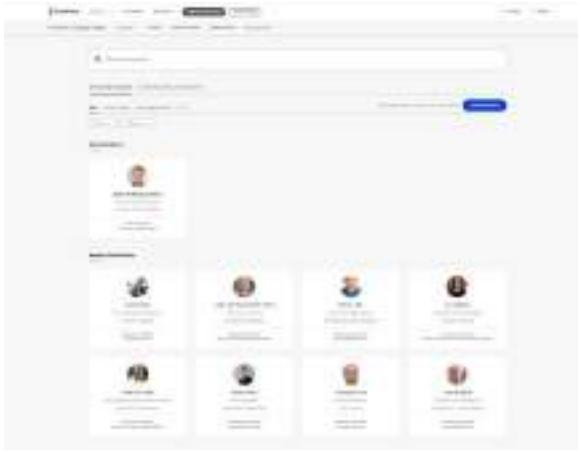

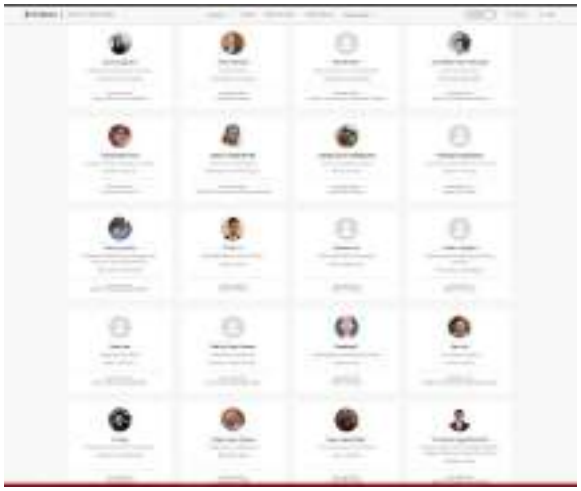

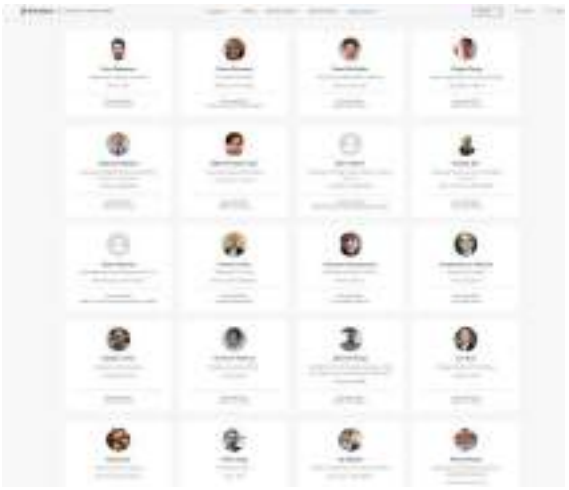

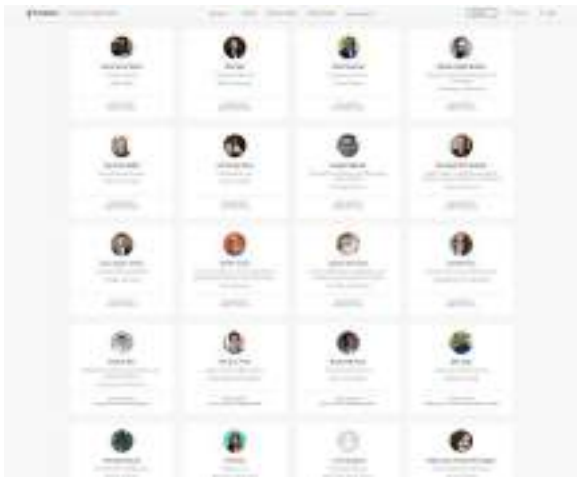

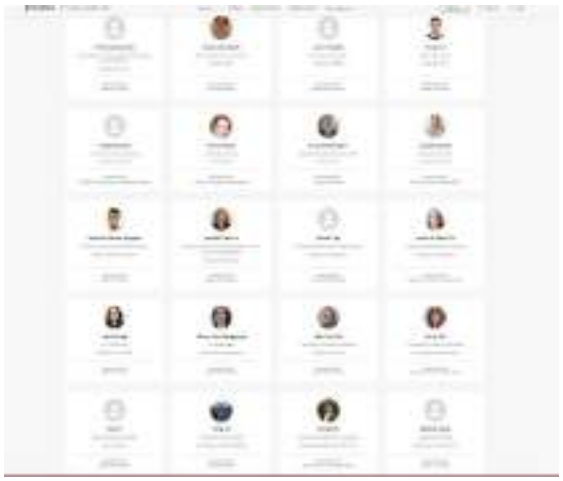

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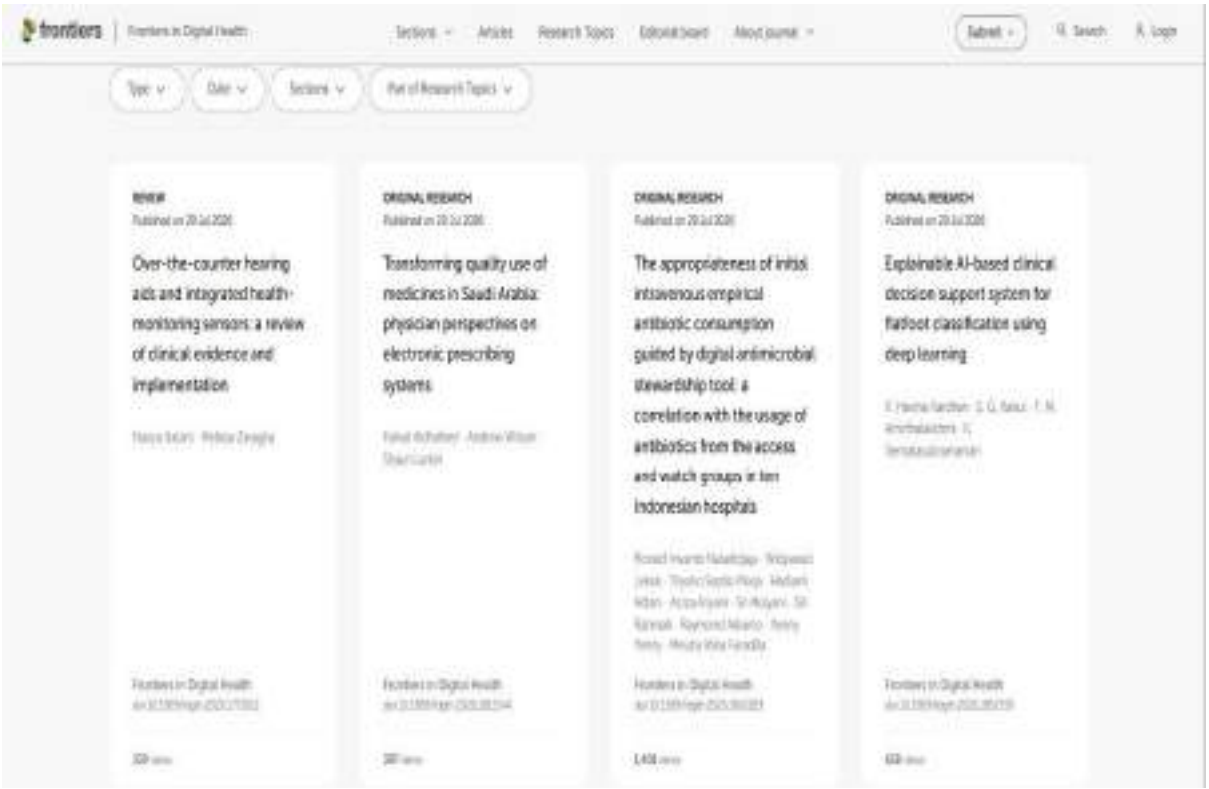

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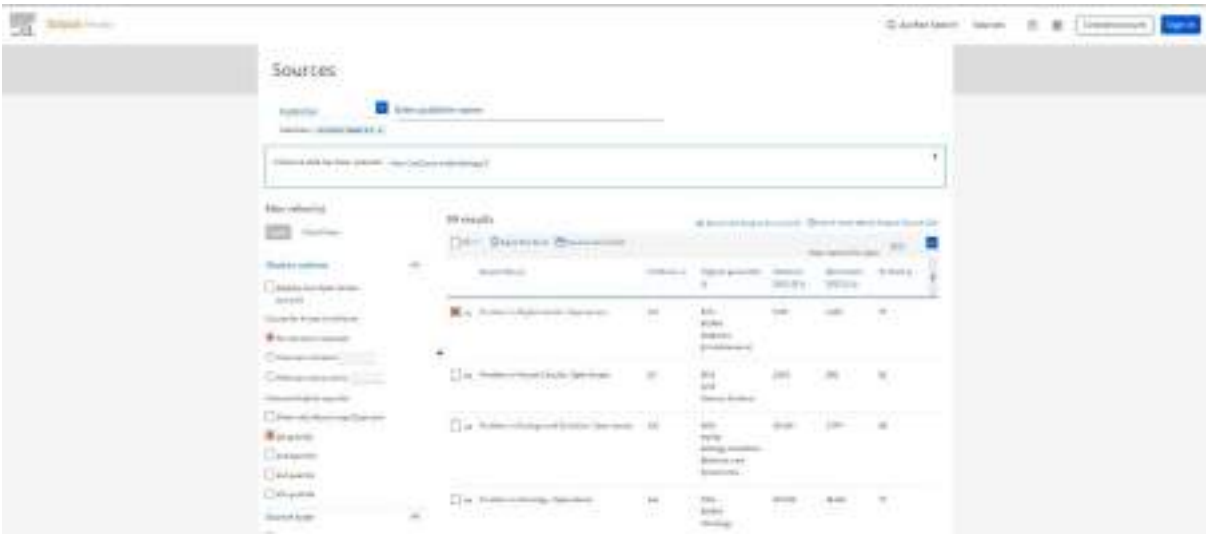
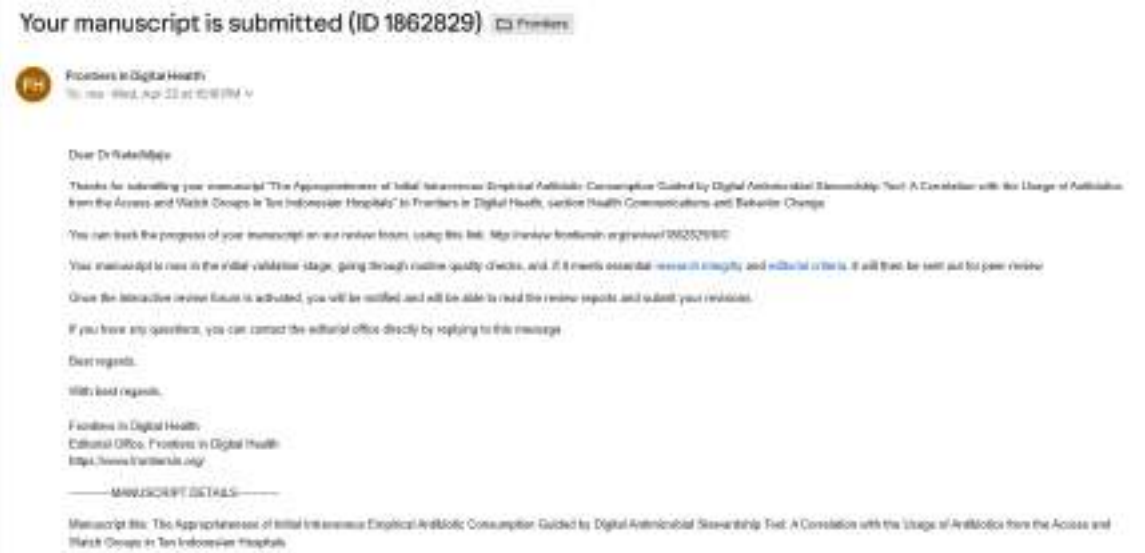


BUKTI KORESPONDENSI



Your manuscript is submitted (ID 1862829) Frontiers

Frontiers in Digital Health

Dear Dr Rakefdjaja

Thanks for submitting your manuscript "The Appropriateness of Initial Intravenous Empirical Antibiotic Consumption Guided by Digital Antimicrobial Stewardship Tool: A Correlation with the Usage of Antibiotics from the Access and Watch Groups in Ten Indonesian Hospitals" to Frontiers in Digital Health, section Health Communications and Behavior Change.

You can track the progress of your manuscript on our review forum, using this link: http://review.frontiersin.org/review/1862829/EN

Your manuscript is now in the initial validation stage, going through routine quality checks, and, if it meets essential research integrity and editorial criteria, it will then be sent out for peer review.

Once the interactive review forum is activated, you will be notified and will be able to read the review reports and submit your revisions.

If you have any questions, you can contact the editorial office directly by replying to this message.

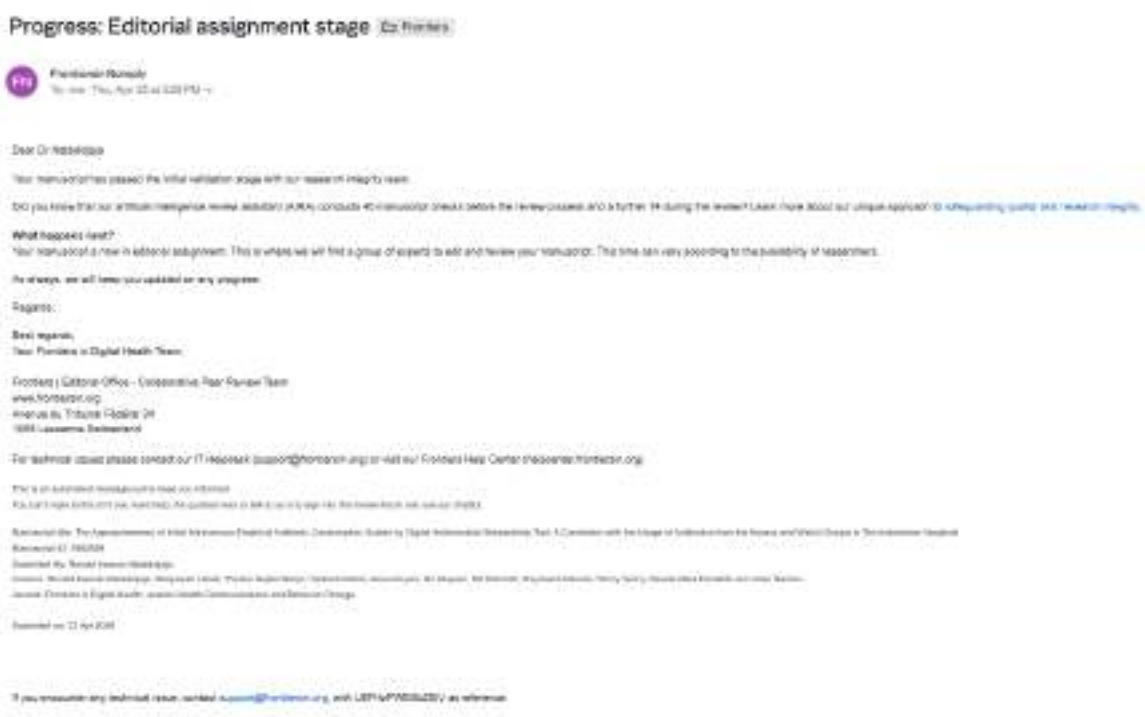
Best regards,

With best regards,

Frontiers in Digital Health
Editorial Office, Frontiers in Digital Health
https://www.frontiersin.org/

---------- MANUSCRIPT DETAILS: ----------

Manuscript title: The Appropriateness of Initial Intravenous Empirical Antibiotic Consumption Guided by Digital Antimicrobial Stewardship Tool: A Correlation with the Usage of Antibiotics from the Access and Watch Groups in Ten Indonesian Hospitals



Progress: Editorial assignment stage Frontiers

Frontiers in Digital Health

Dear Dr Rakefdjaja

Your manuscript has passed the initial validation stage with our research integrity team.

Did you know that our artificial intelligence review assistant (AIRA) conducts 40 manuscript checks before the review process and a further 14 during the review? Learn more about our unique approach to safeguarding quality and research integrity.

What happens next?
Your manuscript is now in editorial assignment. This is where we will find a group of experts to edit and review your manuscript. The time can vary according to the availability of researchers.

As always, we will keep you updated on any progress.

Regards,

Best regards,
Your Frontiers in Digital Health Team

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If a full name is not set, kindly do so in order to align with the Frontiers style.

Manuscript title: The Appropriateness of Initial Intravenous Empirical Antibiotic Consumption Guided by Digital Antimicrobial Stewardship Tool: A Correlation with the Usage of Antibiotics from the Access and Watch Groups in Ten Indonesian Hospitals
Manuscript ID: 1862829
Submitted By: Rahadi Hasnan Rakefdjaja
Journal: Frontiers in Digital Health
Specialty Section: Health Communications and Behavior Change

Submitted on: 22 Apr 2026

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Your manuscript has been added to a Research Topic

Frontiers

Frontiers in Digital Health
To: me · Tue, May 5 at 2:24 PM

Hello Dr. Nabadidjaja,

I'm happy to let you know that your manuscript has been added to the Research Topic Artificial Intelligence and Digital Health Innovations for Communicable Disease Surveillance, Prevention and Control, hosted by Dr. Di Pumpo et al.

Please note that your manuscript remains submitted in *Health Communications and Behavior Change* in *Frontiers in Digital Health*.

As soon as a minimum of two independent review reports are submitted, the handling editor will assess them and will consider the next steps in the peer review process.

Thank you for your consideration. And of course, if you have any questions let me know and I'll be happy to help.

Need an answer quickly? Our AI Assistant, Fronton, is ready to help you in the Review Forum. Fronton can help answer most questions, including status updates and technical questions, as well as advise you on the next steps of the peer review process. Log in to the Review Forum to chat with Fronton today.
Review Forum

FrontiersinNoreply
To: me · Wed, May 13 at 1:36 AM

Dear Dr Nabadidjaja,

Just to let you know, your manuscript "The Appropriateness of Initial Intravenous Empirical Antibiotic Consumption Guided by Digital Antimicrobial Stewardship Tool: A Correlation with the Usage of Antibiotics from the Access and Watch Groups in Ten Indonesian Hospitals" has now moved on to the Independent review stage of the process.

There's nothing you need to do right now. We'll be back in touch when there's another update on your manuscript.

Thanks,

--

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Independent review report submitted (ID 1862829)

Frontiers

Frontiers in Digital Health
To: me · Thu, May 14 at 8:16 PM

Dear Dr Nataclidjaja,

A new report has been submitted by Reviewer 1.

As soon as all reviewers have submitted their comments, you will be able to access the reports in the Review Forum, enabling you to start your revisions.

If you have any questions, the quickest way to contact us is through the chatbot in the Review Forum.

You can track the progress of your manuscript using the button below:

Frontiers in Digital Health
To: me · Tue, May 26 at 6:34 PM

A new report has been submitted by Reviewer 2.

As soon as the reviewers have submitted their comments, you will be able to access the reports in the review forum and start your revisions.

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Your manuscript's review is now active (ID 1862829) Frontiers


Frontiers in Digital Health
To: me · Fri, May 29 at 4:54 PM

Dear Dr Nelwan

The interactive review of your manuscript "The Appropriateness of Initial Intravenous Empirical Antibiotic Consumption Guided by Digital Antimicrobial Stewardship Tool: A Correlation with the Usage of Antibiotics from the Access and Watch Groups in Ten Indonesian Hospitals", submitted to Frontiers in Digital Health, section Health Communications and Behavior Change, has now been activated.

To keep your manuscript moving through the process, please respond by 12 Jun 2020 to all comments raised by the reviewers and editor in the review forum.

If a reviewer has finalized the review and the discussion on the Reviewer tab is closed, you should submit a reply to pending comments in a new thread in the Editor tab. If necessary, you can also submit a revised version of your manuscript (using tracked changes to highlight the revisions).

To access the review forum and respond to the reviewers, just use this link: http://review.frontiersin.org/review/1862829/OO

If you have any questions, you can contact the editorial office directly by replying to this message.

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New Comments in the Interactive Review Forum - 1862829 Frontiers

Frontiers in Digital Health
To: me · Tue, Jun 9 at 10:28 PM

Dear Dr Nalesdjaja,

New comments were posted by the reviewer 1.
Please visit the interactive review forum using the link below and address these comments within the coming week.
https://review.frontiersin.org/review/bootstrap/df9d2006-3d3b-45e6-85de-4bd1481cdad1

You should aim to respond as soon as possible, directly via the online review forum, to all comments in the review reports and editor tab. If appropriate, you can also submit a revised version of your manuscript. We appreciate your timely response.

Remember that there can be more than one iteration between authors and reviewers, and only when all comments by the reviewers are addressed successfully can the review be finalized.
We wish you a successful interactive review, and remain at your disposal for any questions.

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Your manuscript has moved to final review Frontiers

Frontiersin Noreply
To: me · Thu, Jun 11 at 2:54 PM

Dear Dr Nalesdjaja,

Your manuscript "The Appropriateness of Initial Intravenous Empirical Antibiotic Consumption Guided by Digital Antimicrobial Stewardship Tool: A Correlation with the Usage of Antibiotics from the Access and Watch Groups in Ten Indonesian Hospitals" has moved to the 'review finalised' stage.

Next, the associate editor will assess all the review reports, along with the most recent version of your submitted manuscript. If they have questions or comments, they will contact you directly on the Review Forum. Or if they are satisfied, they will provisionally accept your manuscript for publication.

You don't need to do anything at the moment. We'll be in touch again when the associate editor has finished.

Thanks,

--

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Please submit your revised manuscript (ID 1862829) Frontiers

Frontiers in Digital Health
To: me · Thu, Jun 11 at 5:45 PM

Dear Dr Nalesdjaja,

Comments regarding your manuscript "The Appropriateness of Initial Intravenous Empirical Antibiotic Consumption Guided by Digital Antimicrobial Stewardship Tool: A Correlation with the Usage of Antibiotics from the Access and Watch Groups in Ten Indonesian Hospitals" are awaiting your attention on the review forum. Kindly respond using the Editor's tab and submit the revised manuscript by 15 Jun 2026.

This link will take you to the review forum: http://review.frontiersin.org/review/1862829/0/0

It's best to use tracked changes, as this helps to keep the review process running smoothly.

The review process is almost complete, so we're looking forward to receiving your response. However, if you need more time, just click on "Request Extension" on the review forum.

If you have any questions, you can contact the editorial office directly by replying to this message.

Best regards,

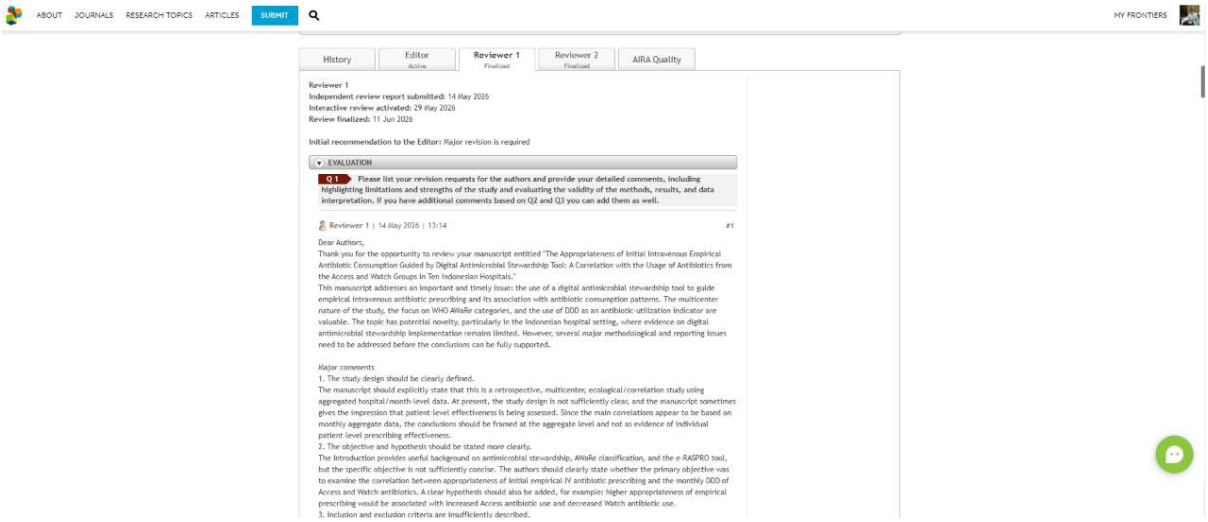
Best regards,

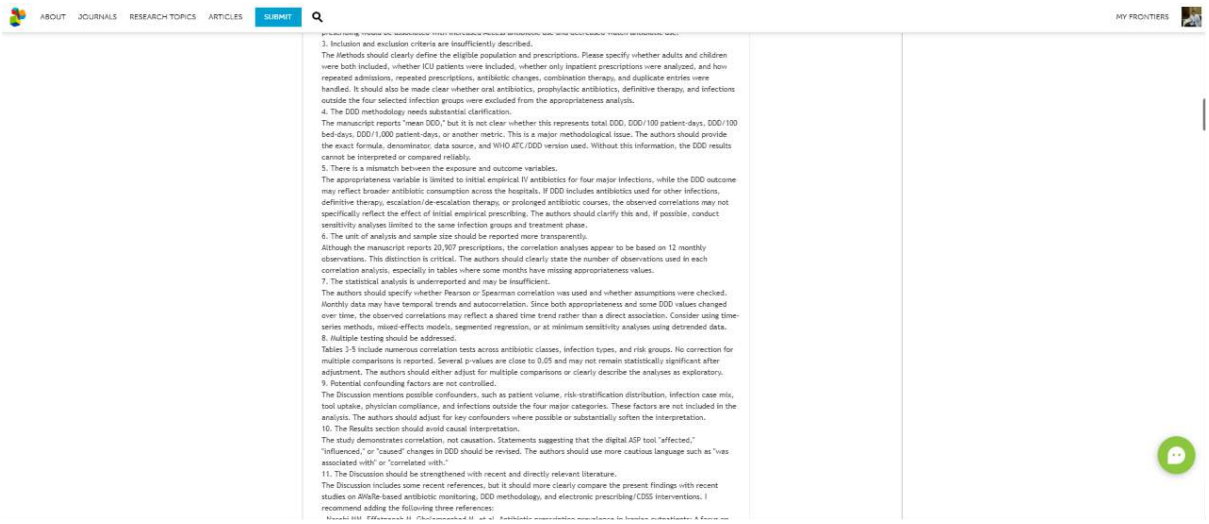
Fantastic news: your article has been accepted Ex Frontiers

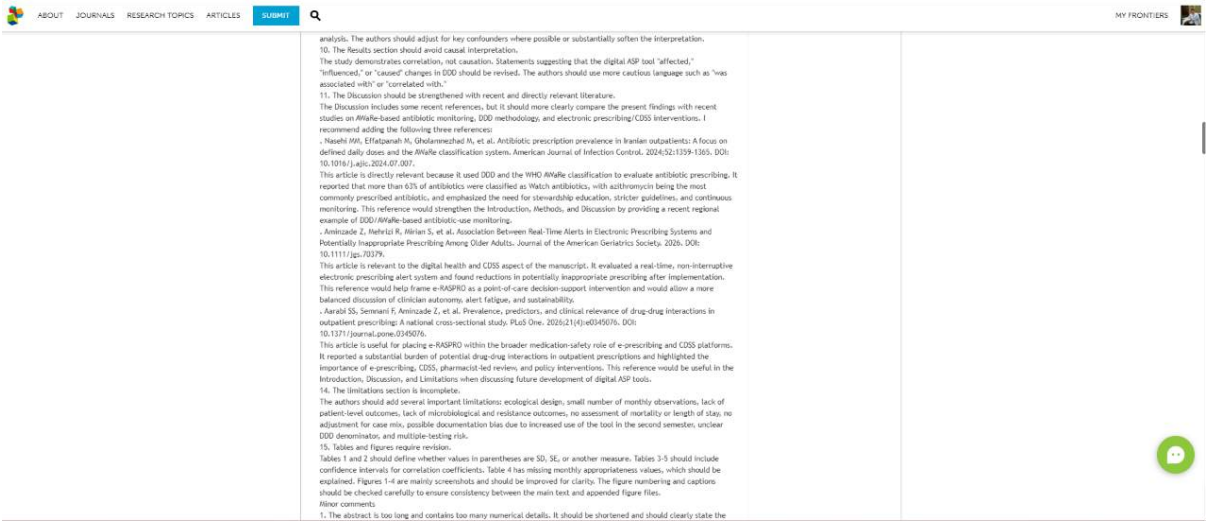
Frontiers in Digital Health

RESPONSE TO REVIEWER'S COMMENT

REVIEWER #1







1. The abstract is too long and contains too many numerical details. It should be shortened and should clearly state the study design.
2. The phrase "antibiotic consumption" is used frequently, but in some parts "antibiotic prescribing" or "antibiotic use" would be more accurate.
3. The sentence stating that Access antibiotics can be prescribed "without any prescription" is confusing. The authors likely mean "without pre-authorization." Please revise.
4. Please standardize terminology throughout the manuscript: "Defined Daily Dose," "DDD," "AWaRe," "Type I/II/III risk stratification," and "third-generation cephalosporins."
5. "Intrabiliary" and "intra-biliary" are used inconsistently. Please use one term consistently.
6. Several grammatical and stylistic issues need correction by a scientific English editor. Examples include "are often become," "may have not been determined," and "has indeed had a correlation."
7. The Methods section contains a long description of the digital tool workflow but lacks essential epidemiological and statistical details. The tool description could be shortened, while the data extraction, denominator definitions, inclusion criteria, and statistical methods should be expanded.
8. The ethical statement says that no patient data were involved, but the study analyzes inpatient prescription data. Please clarify whether data were fully anonymized and aggregated before analysis.
9. Please report confidence intervals for the main correlation coefficients.
10. Please explain why January and March appropriateness values are missing in Table 4 and how these missing values were handled statistically.
11. The conclusion should be more cautious. A possible revised version is:
"In this retrospective multicenter ecological analysis, higher monthly appropriateness of initial empirical IV antibiotic prescribing was associated with higher IV penicillin DDD and lower third-generation cephalosporin DDD. These findings are exploratory and require confirmation in patient-level, controlled studies."

Corresponding Author: Ronald Irwanto Nistadidjaja | 08 Jun 2026 | 14:50 #2

Major comments
1. The study design should be clearly defined.
The manuscript should explicitly state that this is a retrospective, multicenter, ecological/correlation study using aggregated hospital/month-level data. At present, the study design is not sufficiently clear, and the manuscript sometimes gives the impression that patient-level effectiveness is being assessed. Since the main correlations appear to be based on monthly aggregate data, the conclusions should be framed at the aggregate level and not as evidence of individual patient-level prescribing effectiveness.

Response :

Thank you for your very thorough feedback from the peer reviewers. To correct this, we have added the following language to the Abstract - Methods and Research Methods section, point 2.2: This study was a multi-center, retrospective, correlational study using aggregate monthly hospital antibiotic prescription data.

2. The objective and hypothesis should be stated more clearly.

ABOUT JOURNALS RESEARCH TOPICS ARTICLES SUBMIT MY FRONTIERS

2. The objective and hypothesis should be stated more clearly.
The Introduction provides useful background on antimicrobial stewardship, AWaRe classification, and the e-RASPRO tool, but the specific objective is not sufficiently concise. The authors should clearly state whether the primary objective was to examine the correlation between appropriateness of initial empirical IV antibiotic prescribing and the monthly DDD of Access and Watch antibiotics. A clear hypothesis should also be added, for example: higher appropriateness of empirical prescribing would be associated with increased Access antibiotic use and decreased Watch antibiotic use.

Response :

Thank you for your very astute input. To improve this, at the end of the Introduction we have added: This study aims to see the correlation between the mean percentage on the appropriateness of initial intravenous empirical antibiotic consumption based on the Antibiotic Guidelines of the Digital ASP e-RASPRO Tool for the Four Major Infections (Intra biliary Infection, Pneumonia, Urinary Tract Infection, Soft Tissue Infection) with the Mean DDD of Intravenous Antibiotics from the Access and Watch Categories in 2024 at 10 Hospitals. Hypothetically, it is expected that there will be an increase in the use of Access category antibiotics and a decrease in the use of Watch category antibiotics if there is a high appropriateness of empirical prescribing of Initial Intravenous Empirical Antibiotics in Four Major Infections.

3. Inclusion and exclusion criteria are insufficiently described.
The Methods should clearly define the eligible population and prescriptions. Please specify whether adults and children were both included, whether ICU patients were included, whether only inpatient prescriptions were analyzed, and how repeated admissions, repeated prescriptions, antibiotic changes, combination therapy, and duplicate entries were handled. It should also be made clear whether oral antibiotics, prophylactic antibiotics, definitive therapy, and infections outside the four selected infection groups were excluded from the appropriateness analysis.

Response :

Thank you for your insightful input. To improve this, in the Methods section of Point 2.2 in the opening paragraph, we stated the following: The inclusion criteria were initial intravenous empirical antibiotics for all patients (both adults and children) for four major infections during hospitalization. As stated in the title and objectives of this study, subsequent prescriptions or changes in empirical or definitive antibiotics that may occur during treatment were not taken into account.

4. The DDD methodology needs substantial clarification.
The manuscript reports "mean DDD," but it is not clear whether this represents total DDD, DDD/100 patient-days, DDD/100 bed-days, DDD/1,000 patient-days, or another metric. This is a major methodological issue. The authors should provide the exact formula, denominator, data source, and WHO ATC/DDD version used. Without this information, the DDD results cannot be interpreted or compared reliably.

Response :

Thank you for this very important input. To improve this, in the Method section of Point 2.2, in point number 2 regarding Mean DDD, we have added the following sentence: The term DDD referred to here is DDD/100 patient-days,

ABOUT JOURNALS RESEARCH TOPICS ARTICLES SUBMIT MY FRONTIERS

4. The DDD methodology needs substantial clarification.
The manuscript reports "mean DDD," but it is not clear whether this represents total DDD, DDD/100 patient-days, DDD/100 bed-days, DDD/1,000 patient-days, or another metric. This is a major methodological issue. The authors should provide the exact formula, denominator, data source, and WHO ATC/DDD version used. Without this information, the DDD results cannot be interpreted or compared reliably.

Response :

Thank you for this very important input. To improve this, in the Method section of Point 2.2, in point number 2 regarding Mean DDD, we have added the following sentence: The term DDD referred to here is DDD/100 patient-days, which in this manuscript will be referred to as DDD.

5. There is a mismatch between the exposure and outcome variables.
The appropriateness variable is limited to initial empirical IV antibiotics for four major infections, while the DDD outcome may reflect broader antibiotic consumption across the hospitals. If DDD includes antibiotics used for other infections, definitive therapy, escalation/de-escalation therapy, or prolonged antibiotic courses, the observed correlations may not specifically reflect the effect of initial empirical prescribing. The authors should clarify this and, if possible, conduct sensitivity analyses limited to the same infection groups and treatment phase.

Response :

Thank you for the excellent feedback provided by the peer reviewers. We agree that the dependent variable in this manuscript (DDD) could still be influenced by other factors, such as the prescription of further, definitive antibiotics, or antibiotic prescriptions at a wider range of infection sites, which could be confounding factors. However, the p-value we proposed can indicate the extent to which these results are due to chance. The four major infection sites were taken from data from 10 hospitals, which we calculated to cover the majority of infection sites. We did not account for other factors, such as the prescription of further, definitive antibiotics. Therefore, we cannot yet claim that this study is causal. To obtain more comprehensive causal results, further retrospective cohort studies are needed that would include various other factors, such as the prescription of further, empirical, and definitive antibiotics, and the prescription of more infection sites (beyond the four major infections).

6. The unit of analysis and sample size should be reported more transparently.
Although the manuscript reports 20,907 prescriptions, the correlation analyses appear to be based on 12 monthly observations. This distinction is critical. The authors should clearly state the number of observations used in each correlation analysis, especially in tables where some months have missing appropriateness values.

Response :

Thank you for your feedback. Our unit of analysis is monthly data. Our reporting method included monthly data and the number of units analyzed, ensuring transparency.

7. The statistical analysis is underreported and may be insufficient.

7. The statistical analysis is underreported and may be insufficient.
The authors should specify whether Pearson or Spearman correlation was used and whether assumptions were checked. Monthly data may have temporal trends and autocorrelation. Since both appropriateness and some DDD values changed over time, the observed correlations may reflect a shared time trend rather than a direct association. Consider using time-series methods, mixed-effects models, segmented regression, or at minimum sensitivity analyses using detrended data.

Response :

Thank you for your input. The analysis we used was Pearson correlation analysis, following Altman's opinion that a requirement for analysis is that one variable be normally distributed. It's true that our analysis's weakness lies in assuming that each data unit is independent, as Pearson's analysis assumes. However, to reduce the possibility of temporal trends and autocorrelation, we have added our data to present the detrended r, detrended 95% CI (r), and detrended p calculations in Tables 3 and 4, which we then use as the r and p values in the results and discussion sections. Meanwhile, in Tables 3-5, as suggested by the reviewer, we have also included the 95% CI.

8. Multiple testing should be addressed.
Tables 3-5 include numerous correlation tests across antibiotic classes, infection types, and risk groups. No correction for multiple comparisons is reported. Several p-values are close to 0.05 and may not remain statistically significant after adjustment. The authors should either adjust for multiple comparisons or clearly describe the analyses as exploratory.

Response :

Thanks for your input. We will emphasize that this analysis is exploratory due to the extensive analysis undertaken. This way, readers of the journal will also be aware of the exploratory nature of our analysis.

We add note : No adjustment for multiple comparisons was applied. All analyses are exploratory in Tabel 3-5.

9. Potential confounding factors are not controlled.
The Discussion mentions possible confounders, such as patient volume, risk-stratification distribution, infection case mix, tool uptake, physician compliance, and infections outside the four major categories. These factors are not included in the analysis. The authors should adjust for key confounders where possible or substantially soften the interpretation.

Response :

Thank you for your reminder. Given the data collection design and methodology in this manuscript, we acknowledge that it is very difficult to perform various confounding reductions. This is due to the administrative requirements of the hospital that we must comply with when collecting data. Therefore, in the discussion section, we attempt to relax the interpretation and remind readers that this study has not controlled for various confounders such as the number of patients, risk stratification distribution, infection case mix, and infections outside the four major infections.
Therefore, interpretatively, it cannot be said to show a clear causality. To understand further the causal relationship, research with more comprehensive methods and even a larger sample size is needed.

This way, readers of the journal will also be aware of the exploratory nature of our analysis.

We add note : No adjustment for multiple comparisons was applied. All analyses are exploratory in Tabel 3-5.

9. Potential confounding factors are not controlled.
The Discussion mentions possible confounders, such as patient volume, risk-stratification distribution, infection case mix, tool uptake, physician compliance, and infections outside the four major categories. These factors are not included in the analysis. The authors should adjust for key confounders where possible or substantially soften the interpretation.

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Therefore, interpretatively, it cannot be said to show a clear causality. To understand further the causal relationship, research with more comprehensive methods and even a larger sample size is needed.

10. The Results section should avoid causal interpretation.
The study demonstrates correlation, not causation. Statements suggesting that the digital ASP tool "affected," "influenced," or "caused" changes in DDD should be revised. The authors should use more cautious language such as "was associated with" or "correlated with."

Response :

Thank you for your very enlightening statement. Yes, we, as authors, strongly agree that this study does not yet describe a causal relationship. Therefore, in the results section, we use the word "correlation," not "influence," or "cause." Likewise, in the conclusion section, there is one word "influence," which we changed to "correlate with."

11. The Discussion should be strengthened with recent and directly relevant literature.
The Discussion includes some recent references, but it should more clearly compare the present findings with recent studies on AWaRe-based antibiotic monitoring, DDD methodology, and electronic prescribing/CDSS interventions. I recommend adding the following three references:
. Nasehi AM, Effatpanah H, Gholamnezhad M, et al. Antibiotic prescription prevalence in Iranian outpatients: A focus on defined daily doses and the AWaRe classification system. American Journal of Infection Control. 2024;52:1359-1365. DOI: 10.1016/j.ajic.2024.07.007.
This article is directly relevant because it used DDD and the WHO AWaRe classification to evaluate antibiotic prescribing. It reported that more than 63% of antibiotics were classified as Watch antibiotics, with azithromycin being the most commonly prescribed antibiotic, and emphasized the need for stewardship education, stricter guidelines, and continuous monitoring. This reference would strengthen the Introduction, Methods, and Discussion by providing a recent regional example of DDD/AWaRe-based antibiotic-use monitoring.
. Aminzade Z, Mehrtizi R, Mirlan S, et al. Association Between Real-Time Alerts in Electronic Prescribing Systems and Potentially Inappropriate Prescribing Among Older Adults. Journal of the American Geriatrics Society. 2026. DOI: 10.1111/jgs.70379.
This article is relevant to the digital health and CDSS aspect of the manuscript. It evaluated a real-time, non-interruptive electronic prescribing alert system and found reductions in potentially inappropriate prescribing after implementation. This reference would help frame e-RASPRO as a point-of-care decision-support intervention and would allow a more balanced discussion of clinician autonomy, alert fatigue, and sustainability.
. Aarabi SS, Semnani F, Aminzade Z, et al. Prevalence, predictors, and clinical relevance of drug-drug interactions in outpatient prescribing: A national cross-sectional study. PLoS One. 2026;21(4):e0345076. DOI: 10.1371/journal.pone.0345076.
This article is useful for placing e-RASPRO within the broader medication-safety role of e-prescribing and CDSS platforms. It reported a substantial burden of potential drug-drug interactions in outpatient prescriptions and highlighted the importance of e-prescribing, CDSS, pharmacist-led review, and policy interventions. This reference would be useful in the Introduction, Discussion, and Limitations when discussing future development of digital ASP tools.

Response :

Thank you for your very useful suggestions and input. However, there are several considerations from fellow authors: (1). Although the DDD settings and benchmarks are somewhat different (we use an inpatient setting, while Nasehi et al. uses an outpatient setting, we use DDD / 100 patient days, while Nasehi et al. uses DDD / 1000 inhibitants per day), however, according to peer reviewer input, we have added references from the article from Nasehi et al. in the introduction section. For (2) the article by Aminzade Z et al also appears to have a different setting, because this article covers prescribing in geriatric patients and does not discuss antibiotic prescribing specifically, while our manuscript emphasizes prescribing intravenous antibiotic initiation via digital tools, so it is somewhat difficult for our

allow a more balanced discussion of clinician autonomy, alert fatigue, and sustainability.
. Aarabi SS, Semnani F, Aminzade Z, et al. Prevalence, predictors, and clinical relevance of drug-drug interactions in outpatient prescribing: A national cross-sectional study. PLoS One. 2026;21(4):e0345076. DOI: 10.1371/journal.pone.0345076.
This article is useful for placing e-RASPRO within the broader medication-safety role of e-prescribing and CDSS platforms. It reported a substantial burden of potential drug-drug interactions in outpatient prescriptions and highlighted the importance of e-prescribing, CDSS, pharmacist-led review, and policy interventions. This reference would be useful in the Introduction, Discussion, and Limitations when discussing future development of digital ASP tools.

Response :

Thank you for your very useful suggestions and input. However, there are several considerations from fellow authors: (1). Although the DDD settings and benchmarks are somewhat different (we use an inpatient setting, while Nasehi et al. uses an outpatient setting, we use DDD / 100 patient days, while Nasehi et al. uses DDD / 1000 inhibitants per day), however, according to peer reviewer input, we have added references from the article from Nasehi et al. in the introduction section. For (2) the article by Aminzade Z et al also appears to have a different setting, because this article covers prescribing in geriatric patients and does not discuss antibiotic prescribing specifically, while our manuscript emphasizes prescribing intravenous antibiotic initiation via digital tools, so it is somewhat difficult for our writing team to make a linear comparison between our manuscript and this article. (3) The article by Aarabi SS et al. highlights Drug-drug interactions (DDIs) in outpatients, which can generally be reduced by digital prescribing supported by CDSS. However, we also found it somewhat difficult to find a common thread with e-RASPRO, where our manuscript was based on the initiation of intravenous antibiotic prescribing in hospitalized patients. In our opinion, the results of this study are somewhat difficult to use as a comparison in our manuscript, considering the differences in the study scope, background, and research objectives.

14. The limitations section is incomplete.
The authors should add several important limitations: ecological design, small number of monthly observations, lack of patient-level outcomes, lack of microbiological and resistance outcomes, no assessment of mortality or length of stay, no adjustment for case mix, possible documentation bias due to increased use of the tool in the second semester, unclear DDD denominator, and multiple-testing risk.

Response :

Thank you for your excellent input. The scope of this study did not include patient outcomes following antibiotic treatment, including length of stay and mortality, microbiological patterns, and resistance. In accordance with the peer reviewer's input, we also explained in the conclusion that we have changed the word "influence" to "correlate," and this study does not yet describe a cause-and-effect relationship or with comprehensive multiple-testing risk. Meanwhile, we have corrected the DDD in the method section, that the DDD we convey here is DDD / 100 patient days.

15. Tables and figures require revision.
Tables 1 and 2 should define whether values in parentheses are SD, SE, or another measure. Tables 3-5 should include confidence intervals for correlation coefficients. Table 4 has missing monthly appropriateness values, which should be explained. Figures 1-4 are mainly screenshots and should be improved for clarity. The figure numbering and captions should be checked carefully to ensure consistency between the main text and appended figure files.

Response :

Thank you for your attention We have corrected and added these points to this manuscript. For table 1 and table 2 we have added a note that what is in brackets is the Standard Deviation. In table 3-5 we have added the 95% CI of the correlation coefficient. In the explanation of Table 4, we stated that : missing data for January and March was due to administrative issues during data sorting, which suggested a lack of data purity. Therefore, it was decided to exclude data for those months. We have also shifted (i) and (J) after one sentence to avoid confusion for the reader. For figures 1-4 we have increased the image resolution and hopefully it will be clearer.

Minor comments
1. The abstract is too long and contains too many numerical details. It should be shortened and should clearly state the study design.

Response :

Thank you for your input. Yes, we have shortened the abstract and clarified the research design, which we outlined in the methods section of the abstract and in the methods section of the full manuscript, as directed by the reviewer.

2. The phrase "antibiotic consumption" is used frequently, but in some parts "antibiotic prescribing" or "antibiotic use" would be more accurate.

Response :

We have corrected it according to the reviewer's input.

3. The sentence stating that Access antibiotics can be prescribed "without any prescription" is confusing. The authors likely mean "without pre-authorization." Please revise.

Response :

Thank you for your very thorough insight. There is a writing error here, what we mean here is without prior authorization and we have changed it to our manuscript

4. Please standardize terminology throughout the manuscript: "Defined Daily Dose," "DDD," "AWaRe," "Type I/II/III risk stratification," and "third-generation cephalosporins."

Response :

Thank you for your input. Regarding DDD, Risk Stratification Types I, II, and III, and AWARe antibiotics, all of the intended and included in the digital Antibiotic Guidelines in e-RASPRO in this manuscript have been explained in the Methods section. For third-generation cephalosporins, of course, what is meant is all third-generation cephalosporin drugs used in hospitals, and in this study, we calculated this in total, as is the case for other classes of antibiotics.

5. "Intrabiliary" and "intra-biliary" are used inconsistently. Please use one term consistently.

Response :

Thank you, we have fixed it.

6. Several grammatical and stylistic issues need correction by a scientific English editor. Examples include "are often become," "may have not been determined," and "has indeed had a correlation."

Response :

Thank you for your very detailed input. Yes, we have changed "are often become" to "are often overlooked," "may have not been determined" to "has yet to be determined," and "has indeed had a correlation" to "corelated."

7. The Methods section contains a long description of the digital tool workflow but lacks essential epidemiological and statistical details. The tool description could be shortened, while the data extraction, denominator definitions, inclusion criteria, and statistical methods should be expanded.

Response :

Thank you for your input. We intentionally provided a rather lengthy description of this tool to provide readers with a comprehensive overview of its use. We present epidemiological data excerpts in the introduction and discussion for comparison (not in the methods section, which better describes the research methodology). We have also added

7. The Methods section contains a long description of the digital tool workflow but lacks essential epidemiological and statistical details. The tool description could be shortened, while the data extraction, denominator definitions, inclusion criteria, and statistical methods should be expanded.

Response :

Thank you for your input. We intentionally provided a rather lengthy description of this tool to provide readers with a comprehensive overview of its use. We present epidemiological data excerpts in the introduction and discussion for comparison (not in the methods section, which better describes the research methodology). We have also added research design and inclusion criteria to the methods section, under point 2.2 in the first paragraph.

8. The ethical statement says that no patient data were involved, but the study analyzes inpatient prescription data. Please clarify whether data were fully anonymized and aggregated before analysis.

Response :

Thank you. That's right, when extracting data from this device, patient names were omitted.

9. Please report confidence intervals for the main correlation coefficients.

Response :

Thank you for your input, we have included the confidence interval for the correlation coefficient.

10. Please explain why January and March appropriateness values are missing in Table 4 and how these missing values were handled statistically.

Response :

The missing data is due to administrative issues in those months, which we fear could make the data less valid, and therefore, we have not included it. In the explanation of Table 4, we stated that : missing data for January and March was due to administrative issues during data sorting, which suggested a lack of data purity. Therefore, it was decided to exclude data for those months. However, the analysis used is based on the real data. Missing data is not included in the analysis.

11. The conclusion should be more cautious. A possible revised version is:
"In this retrospective multicenter ecological analysis, higher monthly appropriateness of initial empirical IV antibiotic prescribing was associated with higher IV penicillin DDD and lower third-generation cephalosporin DDD. These findings are exploratory and require confirmation in patient-level, controlled studies."

Response :

to exclude data for those months. However, the analysis used is based on the real data. Missing data is not included in the analysis.

11. The conclusion should be more cautious. A possible revised version is:
"In this retrospective multicenter ecological analysis, higher monthly appropriateness of initial empirical IV antibiotic prescribing was associated with higher IV penicillin DDD and lower third-generation cephalosporin DDD. These findings are exploratory and require confirmation in patient-level, controlled studies."

Response :

Thank you, we have corrected it according to the reviewer's instructions, that with the research method in this manuscript, a conclusive conclusion cannot be drawn regarding the causal relationship and further research is still needed.

Review supporting file - 1188018

Reviewer 1 | 09 Jun 2026 | 15:28 #3

Dear Authors,

Thank you for the revised manuscript and for addressing many of the previous comments. The manuscript has improved substantially, and most major concerns have been resolved. However, a few points still require clarification before endorsement.

Please provide more methodological detail on the DDD calculation, including the exact formula, numerator, denominator, source of patient-days, and the WHO ATC/DDD version or national standard used.
Please clarify the remaining inclusion/exclusion details, particularly whether ICU patients were included, how repeated admissions or duplicate prescriptions were handled, and how combination empirical therapy was counted.
Please state more explicitly that the correlation analyses are based on monthly aggregate observations, not individual prescriptions, and report the exact number of monthly observations used in each correlation analysis, especially where missing data occurred.
Please further emphasize in the Discussion/Limitations that the DDD outcome may reflect broader hospital antibiotic use, including definitive therapy, subsequent antibiotic changes, and infections outside the four selected infection groups. This means the findings should remain exploratory and non-causal.
Please clarify whether all patient-level identifiers were removed and whether the data were fully anonymized or de-identified before aggregation and analysis.
Please standardize terminology throughout the manuscript, especially "Defined Daily Dose," "AWaRe," "Type I/II/III risk stratification," and "third-generation cephalosporins."

Corresponding Author: Ronald Irwanto Natadidjaja | 10 Jun 2026 | 08:48 #4

groups. This means the findings should remain exploratory and non-causal.
Please clarify whether all patient-level identifiers were removed and whether the data were fully anonymized or de-identified before aggregation and analysis.
Please standardize terminology throughout the manuscript, especially "Defined Daily Dose," "AWaRe," "Type I/II/III risk stratification," and "third-generation cephalosporins."

Corresponding Author: Ronald Irwanto Natadidjaja | 10 Jun 2026 | 08:48 #4

Dear Reviewer 1.

We thank you again for reminding us of some things we missed.

So please allow us to provide feedback and improvements to your input.

Reviewer Input : Please provide more methodological detail on the DDD calculation, including the exact formula, numerator, denominator, source of patient-days, and the WHO ATC/DDD version or national standard used.

Response :

Thank you for your very thorough feedback.We apologize in advance for the lack of detail in our response to your feedback. We have added information regarding DDD/100 patient-days to Method point 2.2, about the calculation formula. DDD / 100 patient days = Total Antibiotic Used (gram) / WHO DDD x100

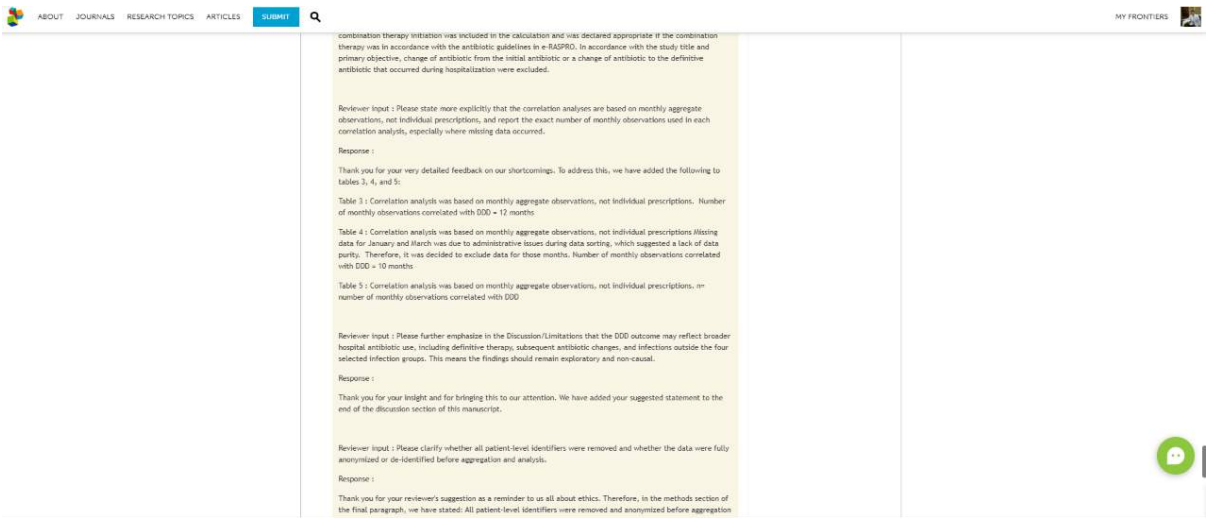
Total Length of Stay

Reviewer Input : Please clarify the remaining inclusion/exclusion details, particularly whether ICU patients were included, how repeated admissions or duplicate prescriptions were handled, and how combination empirical therapy was counted.

Response :

Thank you for your excellent insight. Due to your suggestion we add this statement in the method section point 2.2 first paragraph: The inclusion criteria comprised initial intravenous empirical antibiotics prescribed for all inpatients, both adult and pediatric, including ICU patients, for four major infections. The use of empirical combination therapy initiation was included in the calculation and was declared appropriate if the combination therapy was in accordance with the antibiotic guidelines in e-RASPRO. In accordance with the study title and primary objective, change of antibiotic from the initial antibiotic or a change of antibiotic to the definitive antibiotic that occurred during hospitalization were excluded.

Reviewer Input : Please state more explicitly that the correlation analyses are based on monthly aggregate observations, not individual prescriptions, and report the exact number of monthly observations used in each correlation analysis, especially where missing data occurred.


ABOUT JOURNALS RESEARCH TOPICS ARTICLES SUBMIT
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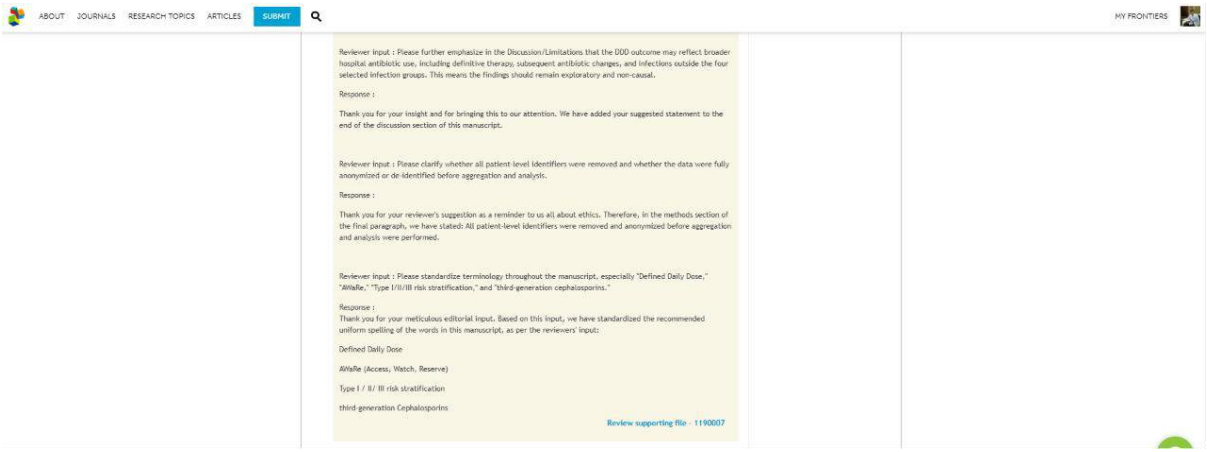
combination therapy initiation was included in the calculation and was declared appropriate if the combination therapy was in accordance with the antibiotic guidelines in e-RASPRO. In accordance with the study title and primary objective, change of antibiotic from the initial antibiotic or a change of antibiotic to the definitive antibiotic that occurred during hospitalization were excluded.
Reviewer Input : Please state more explicitly that the correlation analyses are based on monthly aggregate observations, not individual prescriptions, and report the exact number of monthly observations used in each correlation analysis, especially where missing data occurred.
Response :
Thank you for your very detailed feedback on our shortcomings. To address this, we have added the following to tables 3, 4, and 5:
Table 3 : Correlation analysis was based on monthly aggregate observations, not individual prescriptions. Number of monthly observations correlated with DDD = 12 months
Table 4 : Correlation analysis was based on monthly aggregate observations, not individual prescriptions.Missing data for January and March was due to administrative issues during data sorting, which suggested a lack of data purity. Therefore, it was decided to exclude data for those months. Number of monthly observations correlated with DDD = 10 months
Table 5 : Correlation analysis was based on monthly aggregate observations, not individual prescriptions. n= number of monthly observations correlated with DDD
Reviewer Input : Please further emphasize in the Discussion/Limitations that the DDD outcome may reflect broader hospital antibiotic use, including definitive therapy, subsequent antibiotic changes, and infections outside the four selected infection groups. This means the findings should remain exploratory and non-causal.
Response :
Thank you for your insight and for bringing this to our attention. We have added your suggested statement to the end of the discussion section of this manuscript.
Reviewer Input : Please clarify whether all patient-level identifiers were removed and whether the data were fully anonymized or de-identified before aggregation and analysis.
Response :
Thank you for your reviewer's suggestion as a reminder to us all about ethics. Therefore, in the methods section of the final paragraph, we have stated: All patient-level identifiers were removed and anonymized before aggregation


ABOUT JOURNALS RESEARCH TOPICS ARTICLES SUBMIT
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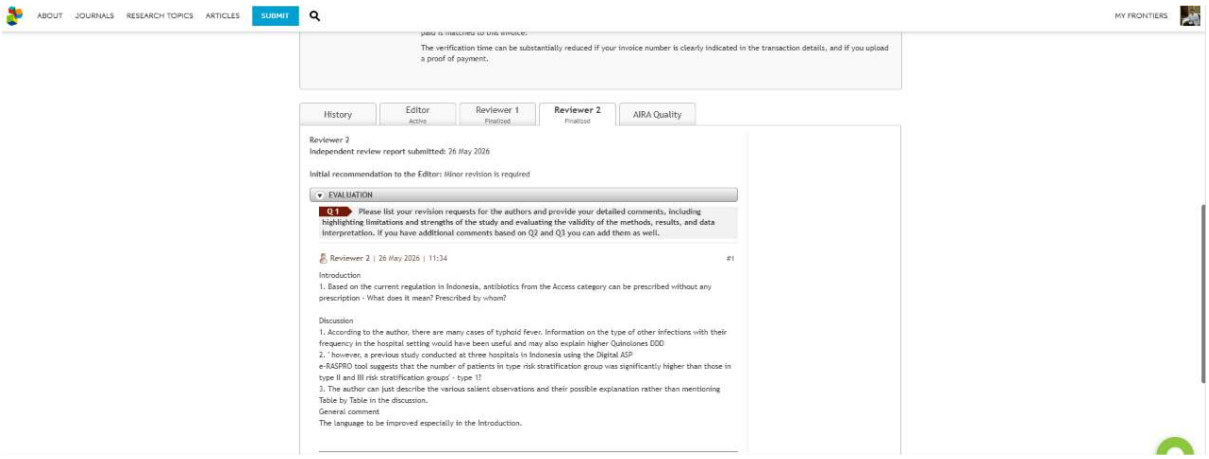
Reviewer Input : Please further emphasize in the Discussion/Limitations that the DDD outcome may reflect broader hospital antibiotic use, including definitive therapy, subsequent antibiotic changes, and infections outside the four selected infection groups. This means the findings should remain exploratory and non-causal.
Response :
Thank you for your insight and for bringing this to our attention. We have added your suggested statement to the end of the discussion section of this manuscript.
Reviewer Input : Please clarify whether all patient-level identifiers were removed and whether the data were fully anonymized or de-identified before aggregation and analysis.
Response :
Thank you for your reviewer's suggestion as a reminder to us all about ethics. Therefore, in the methods section of the final paragraph, we have stated: All patient-level identifiers were removed and anonymized before aggregation and analysis were performed.
Reviewer Input : Please standardize terminology throughout the manuscript, especially "Defined Daily Dose," "AWaRe," "Type I/II/III risk stratification," and "third-generation cephalosporins."
Response :
Thank you for your meticulous editorial input. Based on this input, we have standardized the recommended uniform spelling of the words in this manuscript, as per the reviewers' input:
Defined Daily Dose
AWaRe (Access, Watch, Reserve)
Type I / II/ III risk stratification
third-generation Cephalosporins
Review supporting file - 1190007

REVIEWER #2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The verification time can be substantially reduced if your invoice number is clearly indicated in the transaction details, and if you upload a proof of payment.
History
Editor
Active
Reviewer 1
Finalized
Reviewer 2
Finalized
AIRA Quality
Reviewer 2
Independent review report submitted: 26 May 2026
Initial recommendation to the Editor: Minor revision is required
EVALUATION
Q 1 Please list your revision requests for the authors and provide your detailed comments, including highlighting limitations and strengths of the study and evaluating the validity of the methods, results, and data interpretation. If you have additional comments based on Q2 and Q3 you can add them as well.
Reviewer 2 | 26 May 2026 | 11:34
#1
Introduction
1. Based on the current regulation in Indonesia, antibiotics from the Access category can be prescribed without any prescription - What does it mean? Prescribed by whom?
Discussion
1. According to the author, there are many cases of typhoid fever. Information on the type of other infections with their frequency in the hospital setting would have been useful and may also explain higher Quinolones DDD
2. ' however, a previous study conducted at three hospitals in Indonesia using the Digital ASP
e-RASPRO tool suggests that the number of patients in type risk stratification group was significantly higher than those in type II and III risk stratification groups' - type !!!
3. The author can just describe the various salient observations and their possible explanation rather than mentioning Table by Table in the discussion.
General comment
The language to be improved especially in the Introduction.

Revision request

Editorial Office: Frontiers In Digital Health | 11 Jun 2026 | 08:45 #1

Dear Authors,

To move the process forward we kindly ask you to please reply to Reviewer 2 comments in this thread and re-submit your revisions using the blue 'resubmit manuscript' in the Editor's Tab.

We hope this this message is clear and should you have any other question or need assistance please do not hesitate to get in touch.

Thank you for your time and consideration,
The Editorial Office

Corresponding Author: Ronald Irwanto Natadidjaja | 11 Jun 2026 | 14:03 #1

Dear Editor

Thank you for your attention and suggestions on our manuscript. Here is our response to the suggestion from reviewer 2:

Introduction
1. Based on the current regulation in Indonesia, antibiotics from the Access category can be prescribed without any prescription - What does it mean? Prescribed by whom?

Response:

Thank you for your very thorough insight.

There is a writing error here, what we mean here is without prior authorization and we have changed it to our manuscript.

Discussion
1. According to the author, there are many cases of typhoid fever. Information on the type of other infections with their frequency in the hospital setting would have been useful and may also explain higher Quinolones DDD

Response:

Thank you for your insightful insights.

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Discussion
1. According to the author, there are many cases of typhoid fever. Information on the type of other infections with their frequency in the hospital setting would have been useful and may also explain higher Quinolones DDD

Response:

Thank you for your insightful insights.

It's true that Indonesia is endemic for typhoid fever, and quinolones are indeed the treatment of choice. However, unfortunately, with this research design, and according to the regulations of the hospitals where data were collected, we do not have data on typhoid fever and quinolone use in typhoid from all ten hospitals. Therefore, in the discussion section, we only state assumptions that may or may not be correct. This certainly needs to be tested more comprehensively in further research.

2. ' however, a previous study conducted at three hospitals in Indonesia using the Digital ASP
e-RASPRO tool suggests that the number of patients in type risk stratification group was significantly higher than those in type II and III risk stratification groups' - type 1?

Response:

Thank you very much for your very thorough correction.

Yes, what we meant here was in previous research, the number of patients in type I risk stratification group was significantly higher than those in type II and III risk stratification groups. We've fixed it.

3. The author can just describe the various salient observations and their possible explanation rather than mentioning Table by Table in the discussion.
General comment
The language to be improved especially in the Introduction.

Response:

Thank you for your suggestion. In the discussion section, we have tried our best to explain the interpretation of the tables, although we recognize that this research is correlational and subject to multiple interpretations, and cannot yet establish causality. We have added this explanation to our manuscript in the discussion and conclusion sections. As far as we understand, there is not much research related to digital ASP as a CDSS. However, we have attempted to compare them. Due to this situation, there are certainly many imperfections.

We also attach the items that have been changed according to the input from reviewer 2 (we have changed them from

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2. ' however, a previous study conducted at three hospitals in Indonesia using the Digital ASP
e-RASPRO tool suggests that the number of patients in type risk stratification group was significantly higher than those in type II and III risk stratification groups' - type 1?

Response:

Thank you very much for your very thorough correction.

Yes, what we meant here was in previous research, the number of patients in type I risk stratification group was significantly higher than those in type II and III risk stratification groups. We've fixed it.

3. The author can just describe the various salient observations and their possible explanation rather than mentioning Table by Table in the discussion.
General comment
The language to be improved especially in the Introduction.

Response:

Thank you for your suggestion. In the discussion section, we have tried our best to explain the interpretation of the tables, although we recognize that this research is correlational and subject to multiple interpretations, and cannot yet establish causality. We have added this explanation to our manuscript in the discussion and conclusion sections. As far as we understand, there is not much research related to digital ASP as a CDSS. However, we have attempted to compare them. Due to this situation, there are certainly many imperfections.

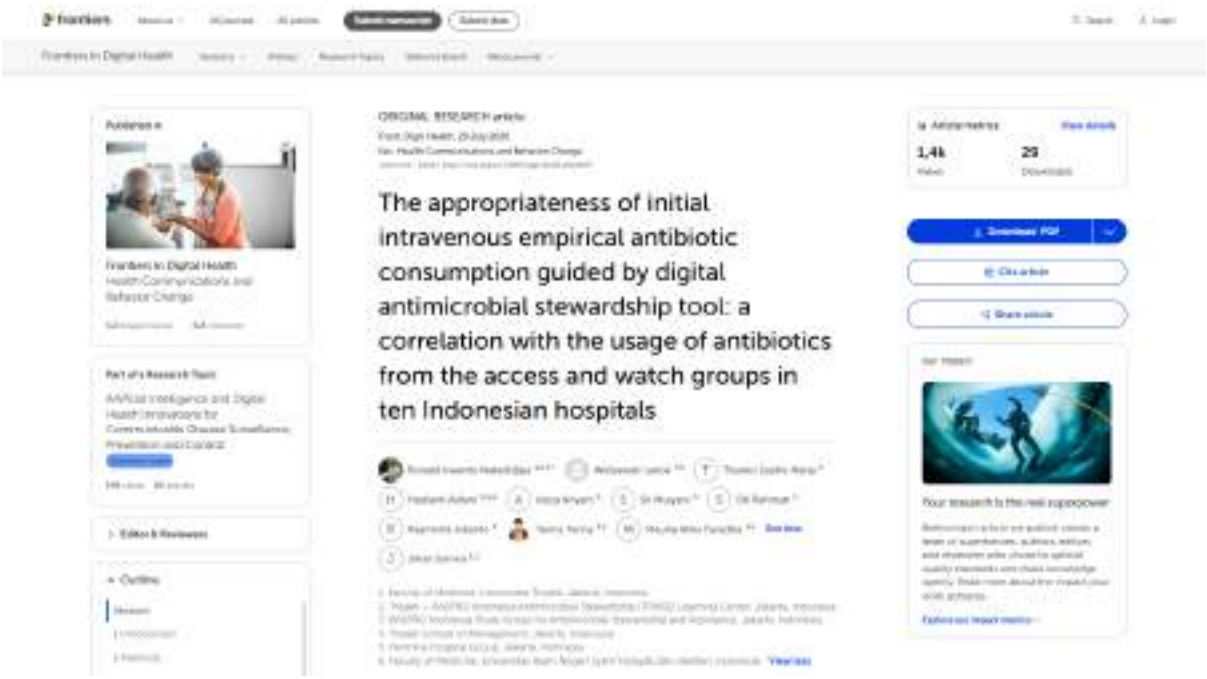
We also attach the items that have been changed according to the input from reviewer 2 (we have changed them from the initial manuscript, but we show these changes through the track changes by highlighting them in blue).

Meanwhile, to emphasize the input given by reviewer 2, which was actually written previously (before the input was given), we have highlighted it in green. Also below are various sentences confirming the analysis in the discussion section (at the end of the discussion) to strengthen the analysis in writing as suggested by reviewer 2. There are several language improvements that we have made, especially related to standardization of writing uniformity which we have also improved, as this was also proposed by reviewer 1. In this regard, fellow editors can see it in the manuscript that we submitted with the previous track changes.

Review supporting file - 240632

RESEARCH ARTICLE

LAMAN: https://www.frontiersin.org/journals/digital-health/articles/10.3389/fdgth.2026.1862829/full



frontiers in Digital Health

TYPE Original Research
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DOI 10.3389/fdgth.2026.1662829

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Front. Digit. Health 8:1662829.
doi: 10.3389/fdgth.2026.1662829

The appropriateness of initial intravenous empirical antibiotic consumption guided by digital antimicrobial stewardship tool: a correlation with the usage of antibiotics from the access and watch groups in ten Indonesian hospitals

Ronald Irwanto Nataadidjaja[1,2,3]*, Widyawati Lekok[3,4], Triyoko Septio Marja[3], Hadlanti Adlani[3,5,6], Azlza Ariyani[3], Sri Mulyani[3], Siti Rahmah[3], Raymond Adlaniso[3], Yenny Yenny[4,7], Meutia Atika Faradilla[1,2] and Jihan Samira[1,2]

[1]Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia, [2]Trisakti – RASPRO Indonesia Antimicrobial Stewardship (TRAISE) Learning Center, Jakarta, Indonesia, [3]RASPRO Indonesia Study Group for Antimicrobial Stewardship and Resistance, Jakarta, Indonesia, [4]Trisakti School of Management, Jakarta, Indonesia, [5]Hermina Hospital Group, Jakarta, Indonesia, [6]Faculty of Medicine, Universitas Islam Negeri Syarif Hidayatullah, Banten, Indonesia

Background: RASPRO Indonesia Study Group for Antimicrobial Stewardship & Resistance has developed a digital antimicrobial stewardship (ASP) tool known as the e-RASPRO, which may provide a guideline for clinical decision on antibiotic prescribing for bacterial infection cases by integrating the WHO AWaRe (Access, Watch, Reserve) classification.

Methods: A multicenter retrospective correlational study was conducted using aggregated monthly hospital antibiotic prescribing data. A correlation test was conducted between the mean percentage on the appropriateness of initial intravenous empirical antibiotic consumption and the mean Defined Daily Dose (DDD) of antibiotics within a year (January to December 2024) in 10 Indonesian hospitals after the socialization of e-RASPRO tool between 2022 and 2024 in four major infections.

Results: There was a significant positive correlation between the mean of percentages on appropriateness of initial intravenous empirical antibiotic consumption in type 1 risk stratification guided by e-RASPRO tool and the mean DDD/100 patient-days of intravenous Penicillin as Access group antibiotic ($r = 0.598$, 95% CI 0.025–0.873, $p = 0.043$) and a significant negative correlation with the mean DDD/100 patient-days of intravenous third-generation Cephalosporins as Watch group antibiotic ($r = -0.632$, 95% CI −0.878 to −0.044, $p = 0.035$) after removed linear temporal trends.

Conclusion: Appropriateness of initial intravenous empirical antibiotic consumption in type I and II risk stratification guided by e-RASPRO tool was correlated with increased consumption of Penicillin as an Access group antibiotic and decreased consumption of third-generation Cephalosporins as a Watch group antibiotic. This study did not describe a causal relationship between the use of the e-RASPRO tool and antibiotic consumption in the hospital.

KEYWORDS

antibiotic, appropriateness, defined daily dose, digital, empirical, intravenous, stewardship

1 Introduction

World Health Organization (WHO) has classified antibiotics into Access, Watch, and Reserve categories. It is expected that the target of antibiotic prescribing from the Access group in various countries may reach at least 60% (1, 2). Supports from hospital management, human resources and other supporting tools are absolutely necessary in order to achieve the WHO target. The implementation of the digital Antimicrobial Stewardship (ASP) may provide good results on the prescribing of antimicrobial agents and it may reduce Defined Daily Dose (DDD) of antibiotics, however, the appropriate digital model has yet to be determined (3–6). The WHO Access, Watch, Reserve (AWaRe) classification can be used as a guideline in consuming antimicrobial agents (6). Based on the current regulation in Indonesia, antibiotics from the Access category can be prescribed without any pre-authorization although appropriate indication would be necessary, while those from the Watch and Reserve groups must be given based on pre-authorization and supervision by the Antimicrobial Stewardship team, infection control consultants and the hospital's Antimicrobial Resistance Control Committee (ARCC) (7). On the other hand, the management and technology of antimicrobial prescribing, as well as the implementation and operational monitoring on the consumption of antimicrobial agents, are often overlooked a part of disparities in the development of National Action Plans (NAPs) (8).

A small-scale survey conducted in 2019, which involved 156 hospital respondents in Indonesia, found that 114 respondents reported that they had not implemented antimicrobial resistance control measures in their hospitals, largely due to the lack of a clear management framework for implementing such measures (9). Another larger survey conducted in Iran from 2022 to 2023 reported that 63% of antibiotics prescribed to outpatients belonged to the WHO Watch category (10). The RASPRO Indonesia Study Group for Antimicrobial Stewardship & Resistance views this as a gap in management, antimicrobial prescribing technology, as well as implementation and operational monitoring that could lead to the failure to implement the ASP in a hospital in Indonesia.

In order to narrow the gap, the RASPRO Indonesia Study Group for Antimicrobial Stewardship and Resistance has developed a Digital ASP tool known as the e-RASPRO, which features digital antibiotic guidelines that classify patients into Types I, II, and III risk stratification based on severity, immune status and medical history. The tool has also integrated the WHO AWaRe antibiotic classification by considering local microorganism pattern (if it is available at the hospital) as well as various considerations that have been evaluated through peer expert review at the hospital. By implementing the tool, it is expected that it can serve as one of modalities to provide a guideline for clinicians as well as monitoring, evaluating and reporting on the administration of prophylactic, empirical, and definitive antibiotics. The Digital ASP e-RASPRO tool can also facilitate on-site consultations between doctors, pharmacists and the hospital's ASP team to coordinate the conduct of prospective pre-authorization audits regarding antibiotic use in the hospital.

This study is expected to serve as a preliminary study involving multiple hospitals with a substantial volume of prescriptions. It aims to examine the correlation between the mean percentage of appropriate initial intravenous empirical antibiotic use, based on the Antibiotic Guidelines of the Digital Antimicrobial Stewardship Program (ASP) e-RASPRO Tool for four major infections (intra-abdominal biliary infection, pneumonia, urinary tract infection, and skin and soft tissue infection), and the mean Defined Daily Dose (DDD) of intravenous antibiotics from the WHO Access and Watch categories in 2024 across 10 hospitals. We hypothesize that a higher rate of concordance with empirical prescribing guidelines for initial intravenous antibiotics in these four major infections will be associated with increased consumption of Access antibiotics and decreased consumption of Watch antibiotics. Nevertheless, we recognize that this study has not clearly explained the cause-and-effect relationship and remains limited to the use of initial intravenous empirical antibiotics, which is associated with antibiotic DDD within a year period of time.

2 Methods

2.1 Early socialization on implementing digital antimicrobial stewardship e-RASPRO tool

Socialization and training program on the Digital ASP e-RASPRO tool was conducted gradually by implementing the digital guidelines for empirical antibiotic therapy at 10 hospitals in Indonesia from 2022 to 2024. The Digital ASP e-RASPRO tool would guide clinicians in deciding on the administration of empirical antibiotics and help hospitals to monitor the appropriateness of the administered antibiotics whether it had been complied with current guidelines.

At these ten hospitals, the digital guidelines for empirical antibiotic therapy outlined in the Digital ASP e-RASPRO tool had been implemented, as agreed upon through peer expert

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reviews at each hospital. In this setting, patients with bacterial infections who would receive empirical antibiotics and would be admitted to an inpatient ward were divided into three risk stratification groups based on their disease severity, immune status, and medical history (5, 11):

- **Type I risk stratification group** is a group of patients with mild bacterial infection, whether immunocompetent or immunocompromised, whose infection do not meet the criteria for Type II and III risk stratification groups; in other words, they are at lower risk of infection with multidrug-resistant (MDR) bacteria.

  Based on the digital guidelines for empirical antibiotic therapy approved through peer expert review by each hospital, in the e-RASPRO tool, this group may receive empirical antibiotics from the Access category, such as Amoxicillin Clavulanate, Ampicillin Sulbactam (Penicillin class – Access) with or without a combination of Amikacin/Gentamicin (Aminoglycoside class - Access). In this risk stratification group, the Quinolone group, which falls under the Watch category, is used in cases of beta-lactam allergy or based on specific clinical considerations.
- **Type II risk stratification group** is a group of patients with mild bacterial infection with the following characteristics: (Immunocompromised AND/OR uncontrolled diabetes mellitus) + (history of antibiotic use within ≤ 90 days AND/OR history of hospitalization at a healthcare facility for 48 h or more (≥ 48 h) but less than 90 days ago (≤ 90 days) AND/OR history of medical device use within ≤ 90 days ago). The group of patients with such characteristics are at risk for infection by MDR bacteria—Extended-Spectrum Beta-Lactamases (ESBLs) (11–17). This group of patients may be prescribed anti-ESBL antibiotics from the Access – Watch category. Based on the digital guidelines for empirical antibiotic therapy approved through peer expert review by each hospital, in the e-RASPRO tool, this group may receive empiric antibiotic treatment of Carbapenem Sparing Agent in order to eradicate ESBLs involving the Access antibiotics, i.e., the combination of Ampicillin Sulbactam/Amoxicillin Clavulanate (Penicillin class - Access) must be combined with Amikacin/Gentamicin (Aminoglycosides class – Access). In this risk stratification group, the Quinolone group, which falls under the Watch category, is used in cases of beta-lactam allergy or based on specific clinical considerations.
- **Type III risk stratification group** is a group of patients with severe/threatening bacterial infection AND/OR patients with Healthcare Associated Infections (HAIs) AND/OR ((Immunocompromised AND/OR uncontrolled diabetes mellitus) + (history of antibiotic use of ≤ 30 days ago AND/OR history of hospitalization at a healthcare facility for 48 h or more (≥ 48 h) but less than 30 days ago (≤ 30 days) AND/OR history of medical device use within ≤ 30 days ago). This group of patients with these characteristics is at high risk of mortality and is also at risk of infection by ESBL bacteria and other multidrug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant *Pseudomonas* spp., and others (11, 18–21). Based on the digital guidelines for empirical antibiotic therapy approved by peer experts at each hospital using the e-RASPRO tool, this group may receive antibiotics in the 'Watch' category, with or without combination therapy using antibiotics in the 'Access' category: Meropenem/Imipenem/Doripenem (Carbapenem class -Watch) with or without a combination of Amikacin/Gentamicin (Aminoglycoside class -Access). In cases of suspected MRSA infection, anti-MRSA antibiotics may be administered. The use of these antibiotics must undergo a pre-authorization process and prospective audit by the hospital's ASP Team. In this risk stratification group, Quinolone group, which falls under the 'Watch' category, are used in cases of carbapenem allergy or based on specific clinical considerations.

The Digital ASP e-RASPRO tool would notify doctors, pharmacists, and nurses regarding the category of antibiotics to be administered (Access, Watch, or Reserve). In accordance with national regulations in Indonesia, if the antibiotic to be used is categorized as Watch or Reserve, the pharmacy is required to consult with the hospital's ASP team, infection control consultant, and hospital ABCC for pre-authorization and prospective audit.

The Digital ASP e-RASPRO tool could be used to guide the selection of initial empirical antibiotics, guide subsequent changes or additions to empirical antibiotic therapy (if necessary), record definitive antibiotic therapy, guide the use of prophylactic antibiotics, issue notifications regarding prolonged antibiotic use, and provide physician notes for difficult-to-treat bacterial infection cases requiring comprehensive discussion. However, in the flowchart below, we have limited the scope to the system that guides physicians in determining the use of initial empirical antibiotics.

The following is a screenshot from the Digital ASP e-RASPRO tool showing the workflow for determining the use of initial empirical antibiotics (the first empirical antibiotics prescribed by a doctor when a patient is admitted to the hospital), using the digital empirical antibiotic guidelines on this device (5).

The Digital ASP e-RASPRO tool is designed to guide and monitor physicians in prescribing antibiotics. Figure 1 shows boxes that can be selected by physicians for antibiotic use in daily practice for hospitalized patients. Box (A) was referred to as the RASAL Box. This box must be checked when the doctor decided to administer initial empirical antibiotics (intravenous or oral). The initial empirical antibiotic was the first antibiotic decided by the doctor to administer for a patient upon admission to the inpatient ward. Box (B) was referred to as the RASLAN Box. This box must be checked when the doctor decided to change the empirical antibiotic regimen during treatment, if necessary. The RASLAN box could be used as a guide for escalating (step-up) or de-escalating (step down) antibiotic treatment based on digital empirical guidelines and the doctor's clinical observations.

Box (C) was referred to as the RASPIAIA Box. This box must be checked and filled out when a doctor decided that there were specific indications requiring prolonged antibiotic administration (whether empirical or definitive). If antibiotic use exceeds a

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FIGURE 1
The doctor's screen served as a guideline on prescribing antibiotic, reporting cases of prolonged antibiotic use and reporting cases of difficult-to-treat bacterial infections. (A) RASAL Box. (B) RASLAH Box. (C) RASPRAJA Box. (D) RASPATUR Box. (E) RASGRASI Box. (F) e-Prophylaxis Box.

certain duration and the doctor failed to check the RASPRAJA Box, the hospital may issue an Automatic Stop Order (ASO).

Box (D) was called the RASPATUR Box. This box must be checked when a doctor prescribed a definitive antibiotic. Box (E) was called the RASGRASI Box. This box can be checked when a doctor would report difficult-to-treat bacterial infection cases, in which the patient had already received multiple changes of antibiotic treatment. When the RASGRASI Box was clicked, a notification would be sent to the pharmacist, and the difficult case could be submitted for a collaborative case review involving the Hospital's ASOC. Box (F) was called the e-Prophylaxis Box, which could be used to guide doctors in the administering prophylactic antibiotics.

After the doctor clicked the RASAL box (A) in Figure 1, the screen advanced to the next phase, as shown in Figure 2. Figure 2 illustrates how the Digital ASP e-RASPRO tool guided the physician in administering initial empirical antibiotics (intravenous or oral) when a patient was admitted to the hospital.

The doctor could input data about the patient's condition based on current clinical observations, including: (1) Severity of illness of the patient's infectious disease (Sepsis/Non-Sepsis, Febrile Neutropenia/Healthcare-Associated Infections/Life-Threatening Organ Perforation/Encephalopathy associated with severe bacterial infection), (2) Immune status (Immunocompetent/immunocompromised), (3) The patient's medical history over the past 30 or 90 days (history of antibiotic consumption, history of hospitalization, and history of medical device use). the Digital ASP e-RASPRO tool would provide doctors with information regarding patient risk stratification in accordance with the various academic citations previously cited (G).

After that, the doctor could continue this workflow by clicking on the patient's site of bacterial infection (H). The digital empirical antibiotic guide would provide initial empirical antibiotic options that could be administered to the patient based on the patient's risk stratification. The empirical antibiotic guide was customized according to the guideline that had been agreed upon through a peer expert review at each hospital (I). The doctor could then select the initial empirical antibiotic, along with the dosage, frequency of administration, and route of administration. Through this screen, the doctor would also immediately receive information on whether the prescribed antibiotic fell under the Access, Watch, or Reserve category (J).

After the doctor submitted the initial empirical antibiotic prescription as shown in Figure 2, the workflow in this system would forward it to the pharmacist for review.

Figure 3 shows the pharmacist's screen, which was used to review the prescribed antibiotics. Through this screen, the pharmacist would be informed of various details, including: (1) Site of infection, (2) Patient risk stratification, (3) Appropriateness of antibiotic prescription based on the digital empirical guidelines (by clicking the 'Guide' button), (4) Type of antibiotic that had been administered, antibiotic category (Access/Watch/Reserve), (5) Dose, frequency and route of administration.

Pharmacists could click the phone icon in the upper-right corner to consult with the hospital's ASP Team on-site if the prescribed antibiotics did not comply with the guidelines AND/OR if the prescribed antibiotics fell under the Watch or Reserve categories. If no agreement had been reached regarding the use of antibiotics among the pharmacist, the hospital's ASP team, and the physician, but the antibiotics must be dispensed immediately for patient safety reasons, the pharmacist may issue a special notification through this system. These notifications could then be submitted to hospital management every three to six months (semester) to serve as a basis for evaluation and to determine future policies regarding the prudent use of antibiotics.

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FIGURE 3
The doctor's screen showing workflow and guideline to determine initial empirical antibiotics. (i) Patient Risk Stratification Guided by e- RASPRO tool. (ii) Determination of the site of bacterial infection by the physician in e- RASPRO tool. (3) Empirical antibiotic guidelines in e- RASPRO. (3) WHO AWaRe antibiotic category notifications in e- RASPRO.

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FIGURE 3
The pharmacist's screen to evaluate antibiotics that had been administered.

FIGURE 4
The nurse's screen to monitor antibiotic use.

Once the pharmacist had completed the assessment of the initial empirical antibiotic prescription as shown in Figure 3, the pharmacist could submit the assessment and the workflow on the system would forward it to the nurse so that they could also monitor antibiotic use.

Figure 4 shows the nurse's screen, in which the nurse could access various pieces of information, namely: (1) the site of the patient's infection, (2) the patient's risk stratification, (3) the appropriateness of antibiotic prescription according to the digital empirical guidelines (by clicking the 'Guide' button), (4) the type of antibiotic that had been administered and the antibiotic category (Access/Watch/Reserve), (5) The dose, frequency and route of administration of antibiotics. Nurses and pharmacists could also monitor how many days the antibiotics were administered. If a doctor prescribed long-term antibiotics, the nurse and/or pharmacist could remind the doctor to document the indication for long-term antibiotic use in the RASPRAJA Box (Figure 1F), because if the indication had not been clearly documented through that box, the hospital might enforce Automatic Stop Order (ASO).

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2.2 Obtaining and analyzing data

This was a multicenter retrospective correlational study using aggregated monthly hospital antibiotic prescribing data. The data were retrospectively collected from inpatient units at 10 hospitals between January and December 2024 using the Digital Antimicrobial Stewardship Program (ASP) e-RASPRO tool. The inclusion criteria comprised initial intravenous empirical antibiotics prescribed for all inpatients, both adult and pediatric, including ICU patients, for four major infections. The use of empirical combination therapy initiation was included in the calculation and was declared appropriate if the combination therapy was in accordance with the antibiotic guidelines in e-RASPRO. In accordance with the study title and primary objective, change of antibiotic from the initial antibiotic or a change of antibiotic to the definitive antibiotic that occurred during hospitalization were excluded. The same empirical antibiotic guideline was in effect at all 10 hospitals, as agreed upon by each hospital's peer expert review committee. Data were retrieved in early 2025, which included the following:

1. Percentage of Appropriate Use of Initial Empirical Intravenous Antibiotics (the first empirical intravenous antibiotic administered upon a patient's admission to the inpatient ward) for the four most common infections (the '4 Major' infections), i.e., Intrabiliary Infections, Pneumonia, Urinary Tract Infection and Pyelonephritis, and Soft Tissue Infection at 10 hospitals between January and December 2024.

The four major infections selected were those that deemed to be highly prevalent in the 10 hospitals, which had been studied during 2024. The consumption of a single initial intravenous empirical antibiotic was categorized as appropriate if it complied with the guidelines in the Digital ASP e-RASPRO tool. The use of a combination of initial intravenous empirical antibiotics was categorized as appropriate if both complied with the guideline in the Digital ASP e-RASPRO tool.

(1) Mean DDD of Intravenous Antibiotics. In accordance with Indonesian national regulations, DDD refers to the Defined Daily Dose/100 patient-days, hereafter termed DDD. *DDD / 100 patient days* =

$$\frac{\text{Total Antibiotic Used (gram) / WHO DDD}}{\text{Total Length of Stay (LOS)}} \times 100.$$

Data about mean DDD for the five largest classes of intravenous antibiotics were collected and calculated from 10 hospitals, specifically for the Access Group (Penicillins and Aminoglycosides) and the Watch Group (third-generation Cephalosporins, Quinolone, and Carbapenem group) between January and December 2024 to observe the trends of antibiotic consumption during that year.

Afterwards, the percentage on the appropriateness of initial intravenous empirical antibiotic consumption based on the digital antibiotic guidelines was described according to patient risk stratification groups for the 4 major infections, as well as the mean DDD of the five classes intravenous antibiotics between the first semester (January to June 2024) and 2nd semester (July to December 2024) during the implementation of the Digital ASP e-RASPRO tool. A correlation analysis was conducted between the mean percentage on the appropriateness of initial empirical intravenous antibiotic consumption based on the digital antibiotic guidelines for the 4 major infections and the mean DDD of intravenous antibiotics in 2024.

All patient-level identifiers were removed and anonymized before aggregation and analysis were performed. Data processing discussions, and various verifications were conducted from mid- to late 2025. The appropriateness of initial intravenous empirical antibiotics consumption and the DDD of intravenous antibiotics were verified by pharmacists from each hospital using the Digital ASP e-RASPRO tool. All data extracted from the Digital ASP e-RASPRO tool was then re-verified by the ARCC and peer experts from the ten hospitals. Data analysis and manuscript writing began in early 2026 under the supervision of the various parties involved in this study.

3 Results

The results of this study are presented in the five tables provided by the researchers. All data were obtained in 2024 from 10 hospitals.

Table 1 shows the total number of initial empirical intravenous antibiotic prescriptions for the four major infections at 10 hospitals, which was recorded in the Digital ASP e-RASPRO tool, which reached 20,907 prescriptions during 2024. During the first semester, about 4,886 prescriptions were documented; while in the second semester, 16,021 prescriptions were recorded. There was an increase in the mean percentage on the appropriateness of initial intravenous empirical antibiotic consumption in the combined type I and II risk stratification group from 65.1% in the first semester to 90.6% in the second semester; while for those in the type III risk stratification group, there was an increase from 63.8% in the first semester to 86.2% in the second semester.

Table 2 shows a sharp increase in the mean DDD for Penicillin-class antibiotics and a decrease for third-generation Cephalosporins. The DDD for Penicillin-class antibiotics increased from 30.648 (7.245) to 47.879 (7.374), while the DDD for intravenous third-generation Cephalosporins consumption decreased from 16.369 in the first semester to 13.071 in the second semester. There was an increase in DDD for aminoglycosides, Quinolone and Carbapenem, but it was not as significant as the increase in DDD for Penicillin.

Table 3 shows a significant correlation between the appropriateness of initial intravenous empirical antibiotic consumption in type I and II risk stratification with the use of intravenous penicillin and third-generation Cephalosporins. After detrending via standardized residuals to remove linear temporal trends, significant positive and negative correlations persisted between the mean percentage on appropriate initial intravenous empirical antibiotics in the combined type I and II risk stratification group and the mean DDD of intravenous Penicillin ($r = 0.548$, 95% CI: 0.021–0.873; $p = 0.041$) and intravenous third-generation Cephalosporin ($r = -0.612$, 95% CI: −0.878 to −0.046; $p = 0.035$). For both antibiotics, the 95% confidence intervals for raw and detrended analyses excluded zero, indicating that month-to-month changes in

TABLE 1 Description on mean percentage of appropriateness on initial intravenous empirical antibiotic consumption in two groups (combined type I and II risk stratification group and type III group) based on the digital ASP e-RASPRO tool guidelines for the four major infections between the first and second semesters in 2024 at 10 hospitals.

Initial intravenous empirical antibiotics for the four major infection	The 1st semester January to June 2024		The 2nd semester July to December 2024		Total
	n	Mean Percentage of Appropriateness (x100%)	n	Mean Percentage of Appropriateness (x100%)	
Total Prescription	6,890		10,222		20,907
Type I + II Risk Stratification		0.651 (0.282)		0.906 (0.018)	–
Type III Risk Stratification		0.838 (0.207)		0.862 (0.160)	–

Values in parentheses are standard deviations.

TABLE 2 Description of the mean daily dose (DDD) of intravenous antibiotics in the first and second semesters following the implementation of the digital ASP e-RASPRO tool in 2024 at 10 hospitals.

Antibiotic class	The 1st semester January to June 2024	The 2nd semester July to December 2024
	Mean DDD	Mean DDD
Penicillin	30.648 (7.243)	47.879 (7.570)
Aminoglycosides	0.807 (0.585)	0.906 (1.525)
Third-generation Cephalosporins	16.369 (1.807)	13.071 (1.391)
Quinolone	27.965 (2.941)	31.336 (1.485)
Carbapenem	6.186 (1.893)	8.469 (5.358)

Values in parentheses are standard deviations.

appropriateness were associated with concurrent changes in antibiotic use independent of overall secular trends.

No significant correlation was found between the mean percentage on appropriate initial intravenous empirical antibiotics in the combined type I and II risk stratification group and the mean DDD of intravenous Quinolone, even though the Quinolone group was used as an alternative antibiotic for this group.

Table 4 shows an insignificant correlation between the variables tested. After detrending via standardized residuals to remove linear temporal trends, correlations between the mean percentage on appropriate initial intravenous empirical antibiotics in the type III risk stratification group and the mean DDD of intravenous remained non-significant and close to zero for both intravenous Quinolone ($r = 0.081$, 95% CI −0.576–0.672; $p = 0.825$) and Carbapenem ($r = -0.177$, 95% CI −0.722–0.547; $p = 0.625$).

Table 5 shows various correlations between appropriateness on initial empirical intravenous antibiotic consumption and DDD of antibiotics in four major infections grouped by risk stratification. In type I + II risk stratification patients, prescribing appropriateness was significantly positively correlated with intravenous Penicillin consumption for pneumonia ($n = 12$; $r = 0.785$, 95% CI 0.377–0.938; $p = 0.002$), urinary tract infection and pyelonephritis ($n = 10$; $r = 0.654$; 95% CI 0.810–0.913; $p = 0.040$), and soft tissue infection ($n = 11$; $r = 0.623$, 95% CI 0.052–0.888; $p = 0.041$). Significant inverse correlations with Watch group antibiotics were observed for intravenous third-generation Cephalosporins in pneumonia ($n = 12$; $r = -0.719$, 95% CI −0.915 to −0.236; $p = 0.008$), urinary tract infection and pyelonephritis ($n = 10$; $r = -0.783$, 95% CI −0.949 to −0.316; $p = 0.007$), and soft tissue infection ($n = 11$; $r = -0.780$, 95% CI −0.931 to −0.309; $p = 0.007$), and for Carbapenem in intrabiliary infection ($n = 9$; $r = -0.699$, 95% CI −0.932 to −0.071; $p = 0.036$).

4 Discussion

The issue on the widespread use of third-generation Cephalosporins in Indonesia has been highlighted in a previous study (29). Other studies in Thailand and Cameroon have also highlighted the issue of third-generation Cephalosporins consumption being the most commonly prescribed antibiotics (30, 31). This might be due to physician's limited knowledge regarding antibiotics, inadequate laboratory facilities and poor institutional policies (31).

The WHO has documented that the third-generation Cephalosporins fall under the Watch group. Meanwhile, as has been explained earlier, WHO has set a target for prescribing antibiotic from the Access category as much as ≥60% of total antibiotic prescriptions. It is expected that the utilization of digital ASP tool may improve institutional policies for monitoring appropriate antibiotic consumption in hospitals. The digital ASP e-RASPRO tool has been implemented at the 10 hospitals since 2022.

Table 1 shows increased prescribing of initial empirical intravenous antibiotics that has been documented on the Digital ASP e-RASPRO tool. This may be due to several factors, such as an increase in the number of patients or improved compliance with the utilization of Digital ASP e-RASPRO tool that may lead to more physicians entering data into this digital device as a result of socialization efforts regarding its use that have been conducted in previous years. Table 1 also shows that the mean percentage on the appropriateness of initial intravenous empirical antibiotic consumption that had been increased from the first semester to the second semester. It is followed by Table 2, which illustrates a sharp increase in mean DDD of intravenous Penicillin-class antibiotics categorized as Access and a decrease in mean DDD of intravenous third-generation Cephalosporins-class antibiotics categorized as Watch group. It appears that there is a shift in the trend here. This may also be

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Table 2 Descriptive and correlation analysis between monthly antibiotic consumption (DDD) and the proportion of antibiotic prescriptions classified as appropriate, stratified by Access, Watch, and Reserve categories.

Months	Appropriateness (≥ 250 %)		Penicillin		Access	Aminoglycoside		Third-generation Cephalosporins		Watch	Quinolone		Carbapenem	
			Mean DDD			Mean DDD		Mean DDD			Mean DDD		Mean DDD	
		r			0.794		0.135		−0.741			−0.198		−0.207
		95% CI			0.359 to 0.939		−0.402 to 0.706		−0.933 to −0.267			−0.668 to 0.488		−0.836 to 0.611
		p			0.001		0.698		0.006			0.603		0.691
		Detrended r			0.598		0.194		−0.852			−0.130		−0.190
		95% CI Detrended r			0.103 to 0.873		−0.494 to 0.689		−0.976 to −0.646			−0.781 to 0.634		−0.676 to 0.491
		Detrended p			0.021		0.548		0.000			0.722		0.709
January	0.1660		2298			8.88		9.96			12.12		7.81	
February	0.2221		2134			9.93		10.45			10.27		8.49	
March	0.5451		2742			9.02		10.42			27.71		6.87	
April	0.4086		1930			8.958		11.97			25.83		6.46	
May	0.3947		3334			9.43		12.97			27.96		8.21	
June	0.4184		3168			8.42		12.74			28.87		8.48	
July	0.8807		4874			8.29		12.89			31.03		8.31	
August	0.8012		4238			8.83		14.42			30.24		10.78	
September	0.0691		3334			8.958		14.38			29.41		10.85	
October	0.8862		4630			8.997		12.89			31.44		10.65	
November	0.4960		3810			9.33		12.87			30.71		10.90	
December	0.3084		4130			9.93		11.26			30.83		9.93	

r, Pearson correlation coefficient; CI, confidence interval; p, two-tailed significance value; 95% CI calculated via Fisher Z transformation; Z = 0.5 × ln((1 + r)/(1 − r)); SE = 1/√(n − 3); 95% CI in Z = Z ± 1.96 × SE; back-transformed to r. Computed using SPSS v26 (IBM Corp., Armonk, NY, USA). Detrended r = Pearson correlation of residuals from linear regression of each variable on sequential month (1–12). 95% CI for detrended r calculated using Fisher Z transformation. Detrended p = two-tailed significance of detrended correlation. Asterisk (*) = Pearson correlation is significant at the 0.05 level (two-tailed). Double asterisk (**) = Pearson correlation is significant at the 0.01 level (two-tailed). Number of months contributing to correlation = 12 for all variables. No adjustment for multiple comparisons was applied. All values rounded to 4 decimal places. Number in each cell corresponds with data type and analysis were rounded to the nearest hundredth.

TABLE 3 Descriptive and correlation of the mean percentage on the appropriateness of initial intravenous empirical antibiotics in the type III risk stratification group based on the antibiotic guidelines of the digital ASP e -RASPRO tool for the five major infectious cases with the major DDD of intravenous quinolone and carbapenem in 2024 at 10 hospitals.

Months	Appropriateness (x 100%)		Watch			
			Quinolone		Carbapenem	
			Mean DDD		Mean DDD	
		r		0.128		−0.212
		95% CI[a]		−0.342 to 0.498		−0.710 to 0.388
		P		0.724		0.557
		Detrended, r[b]		0.081		−0.177
		95% CI Detrended, r[b]		−0.376 to 0.672		−0.722 to 0.587
		Detrended, p[b]		0.824		0.631
January	–		32.52		7.85	
February	0.2500		30.17		9.69	
March	–		27.70		4.87	
April	0.5625		25.65		5.80	
May	0.8180		37.06		6.21	
June	0.8951		24.47		8.69	
July	0.8828		31.00		9.11	
August	0.9028		34.26		10.78	
September	0.8286		30.91		10.80	
October	0.8079		31.66		10.83	
November	0.8556		31.75		10.38	
December	0.9462		30.62		9.80	

r, Pearson correlation coefficient; CI, confidence interval; p, two-tailed nominal p-value; 95% CI calculated via Fisher Z transformation; Z = tanh(r) = 0.5[ln(1 + r) − ln(1 − r)]; SE = 1/√(n − 3) = 0.333; 95% CI for Z = Z ± 1.96 × SE, back-transformed to r. Computed using SPSS v29 CORRELATIONS/PARTIAL CORR. Detrended r = Pearson correlation of standardized residuals (ZRESID) from separate linear regressions of each variable on sequential month (1=JAN, 2=FEB, …, 10=OCT; NOV/DEC EXCLUDED). Correlation analysis was based on monthly aggregate observations, not individual prescriptions. Missing data for January and March was due to administrative issues during data sorting, which suggested a lack of data parity. Therefore, it was decided to exclude data for these months. Number of monthly observations correlated with DDD = 10 months. No adjustment for multiple comparisons was applied. All analyses are exploratory.

[a]Assessed by artificial Intelligence with data input and analysis were verified by the authors supported by statistician.

due to the socialization or awareness campaigns regarding the utilization of the tool that have been conducted in previous years that are associated with the WHO AWaRe initiatives.

The shift in prescribing trends toward antibiotics in the Access group (Intravenous Penicillin) appears to be gaining momentum; however, there has also been increased consumption in other antibiotics classified as the Watch group, namely the intravenous Quinolone and Carbapenem classes. Regarding the increased antibiotic consumption, intravenous Quinolone and Carbapenem should be considered along with other biases such as increased number of patients in the 2nd semester, an increase in the number of patients classified in type III risk stratification group, or an increase in the number of patients with infections who are excluded from those with the four major infections, as well as an increase in the number of physicians prescribing intravenous Quinolones as an alternative antibiotic across all three stratification groups.

According to the antibiotic guideline in the Digital ASP e-RASPRO tool developed for the 10 hospitals, antibiotics from the Access group of the Penicillin class – such as Ampicillin Sulbactam and Amoxicillin Clavulanate in combination with Amikacin or Gentamicin—are indeed designated as antibiotics for patients in type I and II risk stratification groups. A previous study conducted at three hospitals in Indonesia found that more than 80% of patients fell into type I risk stratification group (32). If the same pattern holds true in this study, it could still influence a shift in antibiotic prescribing trends, particularly from the Watch Category to the Access Category.

According to the antibiotic guideline in the Digital ASP e-RASPRO tool, patients classified in the type I risk stratification group are empirically recommended to receive antibiotics from the Penicillin class (Ampicillin-Sulbactam or Amoxicillin-Clavulanate) with or without a combination of Aminoglycoside, namely Amikacin or Gentamicin. The intravenous third-generation Cephalosporins have been intentionally excluded from the list of antibiotics for patients in the type I risk stratification group in order to prevent a surge in prescriptions for intravenous third-generation Cephalosporins, which are classified as Watch Category antibiotics.

For the type II risk stratification group, empirical treatment guidelines recommend administering antibiotics from the Access Category of the Penicillin Class—specifically Ampicillin Sulbactam or Amoxicillin Clavulanate— which must be used in combination with an Aminoglycoside, such as Amikacin or Gentamicin. This combination is used as a Carbapenem Sparing Agent, as agreed upon by peer experts from the ten hospitals, to treat patient groups at higher risk of ESBL infections.

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TABLE 3 Pre-correlation multivariate analysis of the association between socioeconomic status and clinical outcomes in patients with type 2 diabetes mellitus and hypertension.

Type of Infection	Appropriateness			Pentoxifylline			Aminophylline			Oral-piperacillin Ceftriaxone Tazobactam			Quinolones			Carbapenem		
		n	t	95% CI*	p	t	95% CI*	p	t	95% CI*	p	t	95% CI*	p	t	95% CI*	p
Urinary Tract Infection and Pyelonephritis	Type I + II Risk Stratification	19	4.434	4.658 to 0.453	0.868	6.110	−4.333 to 0.806	0.195	−4.780	−4.949 to −4.164	0.887	−4.340	−4.777 to 0.998	0.266	−4.647	−4.934 to 0.998	0.847
	Type III Risk Stratification	8										−0.214	−4.791 to 0.832	0.656	−0.479	−0.888 to 0.115	0.228
Soft Tissue Infection (Diabetic Foot/Ulcer Burst)	Type I + II Risk Stratification	11	8.421	8.852 to 0.888	0.861	8.166	+8.338 to 8.118	0.168	−8.768	−8.918 to −8.308	0.887	−8.296	−8.761 to 8.268	0.377	−8.851	−8.410 to 0.501	0.873
	Type III Risk Stratification	9										0.228	−0.004 to 8.178	0.054	−8.887	−0.762 to 0.685	0.824

*Denotes correlation coefficients (CI—confidence interval); p, two-tailed monetary value; 4 gram pentoxifylline data missing for seven months (DOD data completeness = 1.0 for all drugs); IRA (1) calculated via Hubert 2 transformation: Z = 0.5 × ln((1 + r)/(1 − r)); SE = 1/√(n − 3); 95% CI for Z = Z ± 1.96 × SE; back-transformed to r. Computed using SPSS (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.) and MATLAB (R2021b, MathWorks, Natick, MA). Correlations were calculated on monthly aggregated observations, accounting for potential autocorrelation within patients. Multivariate regression models adjusted for age, sex, and baseline severity of infection. Statistical significance was set at $p < 0.05$. All analyses were performed with SPSS (v. 28) and custom MATLAB scripts (see Supplementary Materials). Multiple comparisons were corrected using the Benjamini–Hochberg false discovery rate procedure. Sensitivity analyses were conducted with DOD (no substitution for multiple comparisons applied). All analyses are reported.

Statistical significance was determined by the software as reported in the Supplementary Materials.

The agreed-upon antibiotic guidelines in the Digital ASP e-RASPRO tool has suggested that Carbapenem antibiotics should not be used empirically for patients in the type II risk stratification group (patients at risk for DSBI infections), with the aim of preventing a surge in empirical carbapenem prescriptions in daily practice.

Meanwhile, the Quinolone class antibiotic is still considered appropriate to be used as an alternative empirical treatment in all risk stratification groups, particularly in case of beta-lactam allergy or based on other clinical considerations. Since the same empirical antibiotics are used in both risk stratification groups, in Table 3 we have combined type I and II risk stratification group and correlated them with the mean DDD of each antibiotic class.

Table 3 The persistence of significant detrended correlations between the mean percentage on appropriate initial intravenous empirical antibiotics in the combined type I and II risk stratification group and the mean DDD of intravenous Penicillin ($r = 0.588$, 95% CI: 0.025–0.873; $p = 0.041$) and intravenous third-generation Cephalosporins ($r = -0.612$, 95% CI: −0.878 to −0.044; $p = 0.035$) provides robust evidence that e-RASPRO implementation is correlated with trend shifting from Watch to Access antibiotics beyond general time trends. The consistency of significant associations before and after detrending, with confidence intervals excluding trivial effects, indicates that e-RASPRO is associated with meaningful shifts toward WHO AWaRe-aligned prescribing behavior. Patient-level interrupted time-series analysis are warranted to confirm individual-level mechanisms. This study did not calculate the number of patients in each of the risk stratification groups (type I, II, and III); however, a previous study conducted at three hospitals in Indonesia using the Digital ASP e-RASPRO tool suggests that the number of patients in type I risk stratification group was significantly higher than those in type II and III risk stratification groups (32). If the same pattern occurs in this study, then the appropriateness of early intravenous empirical antibiotic consumption in type I risk stratification group will likely to have a greater influence on the correlation of the mean DDD of intravenous Penicillin with third-generation Cephalosporins antibiotics compared to those in type II risk stratification group.

The lack of a significant positive correlation between the mean percentage on the appropriateness of initial intravenous empirical antibiotic consumption in the combined type I and II risk stratification group for the four major infections and the mean DDD of *Aminoglycoside antibiotics* ($r = 0.384$, 95% CI: −0.539–0.688; $p = 0.568$) may exist due to the fact that Aminoglycoside antibiotics has not been the preferred antibiotic of choice for physicians in daily clinical practice compared to penicillin antibiotics. In addition, Quinolone and Carbapenem are classified as Watch group antibiotics, in which a significant negative correlation is also expected. The Quinolone class can still be considered empirically appropriate for patients in type I and II risk stratification groups; however, its role has been marginalized as alternative antibiotic treatment.

The absence of a significant negative correlation between the mean percentage on the appropriateness of early intravenous empirical antibiotic consumption in the combined type I and II risk stratification group for the four major infections and the mean DDD of intravenous Quinolone antibiotics may be due to the fact that some physicians still consider prescribing intravenous Quinolone antibiotics as an alternative for patients classified in the combined type I and II risk stratification group based on specific clinical considerations, which can actually still be considered appropriate for them. However, the likelihood of using antibiotics from the intravenous Quinolone class here is not as high as that of those the intravenous Penicillin class. These findings may also indicate that the Penicillin class is the preferred class of antibiotics compared to the Quinolone class.

The consumption of Intravenous Quinolone antibiotics for patients in type III risk stratification group, as well as the frequent switching of empirical antibiotic treatment or the switch into definitive antibiotic treatment using antibiotics from Quinolone class, may also be considered as potential causes that warrant further investigation. It may affect the mean DDD of quinolone antibiotics and influence the correlation among variables. Another possible reason for these results is the high number of cases of infections other than the 'major four' that are treated with Quinolone. Indonesia is a tropical country with many cases of typhoid fever or salmonellosis, for which the quinolone class is known as the primary empirical antibiotic of choice. These factors should be considered as potential influences on the mean DDD of Quinolone antibiotics.

The absence of a significant negative correlation between the mean percentage on the *appropriateness* of initial intravenous empirical antibiotic consumption in the combined type I and II risk stratification group for the four major infections and the mean DDD of Carbapenem-class antibiotics may also be influenced by the empirical carbapenem-class antibiotics consumption for patients in type III risk stratification group or other factors. Other reasons also need to be considered, such as the large number of clinicians prescribing carbapenem antibiotics based on culture results. However, more comprehensive research is needed to understand this more clearly.

Table 4 describes the correlation between the mean percentage on the appropriateness initial intravenous empirical antibiotic consumption in type III risk stratification group for the four major infections and the mean DDD of intravenous Quinolone and Carbapenem antibiotics. As previously explained, Carbapenem-class antibiotics, with or without combination therapy with Aminoglycoside-class antibiotics, are the recommended intravenous empirical antibiotic treatment in antibiotic guidelines mentioned the Digital ASP e-RASPRO tool for patients in the type III risk stratification group. Meanwhile, Quinolone-class antibiotics are used as alternative empirical antibiotic treatment in cases of Carbapenem allergy or based on other clinical considerations. Actually, these findings do not indicate a significant positive correlation between the appropriateness of initial intravenous empirical antibiotic consumption in type III risk stratification group for the four major infections and the mean DDD of intravenous Quinolone ($r = 0.081$, 95% CI: −0.576–0.672; $p = 0.825$) and Carbapenem ($r = -0.177$, 95% CI: −0.722–0.587; $p = 0.625$).

The utilization of Quinolone-class antibiotics in this group is still considered appropriate, even though Quinolone are considered as alternative antibiotics in this risk stratification group. Various analyses of other possibilities also need to be conducted, such as the potential use of quinolones in type I and

II risk stratification groups as alternative antibiotic treatment or other factors that could affect the mean DDD of intravenous Quinolone.

A previous study using the Digital ASP e-RASPRO tool at three hospitals in Indonesia over a three-month period has shown that only about 14% of patients fall into type III risk stratification group III [32]. If this were also the case in this study, then the number of patients requiring carbapenem-class antibiotics as initial empirical intravenous treatment would actually be quite small. This could certainly be a factor that may affect mean DDD of Carbapenem-class antibiotics. However, this certainly requires further research. However, it turns out that no significant correlation was found between the mean percentage on the appropriateness initial intravenous empirical antibiotic consumption in type III risk stratification group for the four major infections and the mean DDD of intravenous Quinolone and Carbapenem antibiotics, although the recommended antibiotic in this group of risk stratification is Carbapenem.

Table 5 provides robust statistical evidence that e-RASPRO implementation was correlated with shifting from Watch to Access antibiotics in infections where the shifting is guideline-concordant. The significant inverse correlation between the mean percentage on appropriate initial intravenous empirical antibiotics in the type I and II risk stratification group and the mean DDD of intravenous Carbapenem for intrabiliary infection ($n = 9$; $r = -0.699$, 95% CI −0.932 to −0.071; $p = 0.036$) reflects baseline empiric carbapenem use for type I and II risk stratification for intrabiliary infection was successfully de-escalated post e-RASPRO tool guidance.

In contrast, the mean percentage on the appropriateness of initial intravenous empirical antibiotics in the combined type I and II risk stratification group for intrabiliary infection was not correlated with the mean DDD of intravenous Penicillin and intravenous third-generation Cephalosporins. In this regard, various possibilities should be evaluated further.

In the pneumonia, urinary tract infection and pyelonephritis and soft tissue infection groups, there was a similar pattern to that described in Table 3. The results showed a significant positive correlation between suitability in type I and II risk stratification with DDD intravenous Penicillin and a significant negative correlation between suitability in type I and II risk stratification with DDD intravenous third-generation Cephalosporins.

In this manuscript, the DDD results may reflect broader hospital antibiotic use, including definitive therapy, subsequent antibiotic changes, and infections outside the four selected infection groups. This means the findings should remain exploratory and non-causal. Further investigation is also necessary regarding how many cases that need continuation of initial intravenous empirical antibiotics treatment to achieve patient recovery, or the treatment should be continued based on culture results, which would indicate that the initial intravenous empirical antibiotics administered are indeed effective in treating the patient. Certainly, such factors may also explain the correlation between the appropriateness of initial intravenous empirical antibiotic consumption and the mean DDD of antibiotics. This study does not control for several confounding factors, including patient volume, risk stratification distribution, case mix of infections, and infections other than the four major infections. Results must be interpreted cautiously. The analysis utilized 12-month aggregated data per infection type, and the potential for temporal confounding within each subgroup cannot be excluded, as demonstrated in the overall time-series sensitivity analysis. Therefore, these correlations should be considered hypothesis-generating rather than confirmatory of a causal relationship between e-RASPRO-guided appropriateness and antibiotic consumption patterns. Further research using more comprehensive methods is needed to establish causal relationships.

However, with these preliminary results, it is hoped that the utilization of the Digital ASP e-RASPRO tool can be an intervention in order antimicrobial stewardship program. Digital health technologies that can optimize the consumption of antimicrobial agents and can minimize the impact of healthcare on antimicrobial resistance have the potential to support development and utilization of high-quality data, which are highly beneficial for clinical management and improvement of decision-making [33].

5 Conclusion

Use of the e-RASPRO as a digital antimicrobial stewardship tool was correlated with increased intravenous Penicillin consumption and decreased third-generation Cephalosporins consumption. For patients stratified as risk types I and II, compliance was significantly correlated positively with intravenous Penicillin DDD and negatively with intravenous third-generation Cephalosporins DDD in pneumonia, urinary tract infections and pyelonephritis, and soft tissue infections. Further research using more comprehensive methods is needed to establish a causal relationship.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Research Ethics of Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia, Reference Number 024/KEB/FK/II/2025. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

RN: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. WL: Data curation, Formal analysis, Project administration, Supervision, Writing – review & editing. TM: Data curation, Project administration, Resources, Writing – review & editing. HA: Data curation, Investigation, Writing – review & editing. AA: Investigation, Project administration, Writing – review & editing. SM: Resources, Supervision, Writing – review & editing. SR: Resources, Supervision, Writing – review & editing. RA: Data curation, Software, Writing – review & editing. TY: Supervision, Writing – review & editing. MF: Supervision, Writing – review & editing. IS: Supervision, Writing – review & editing.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in some statistical calculations in this manuscript (as noted in several tables) due to software deficiencies. All data input, analysis, and conclusions were verified by authors and with the assistance of a statistician. The research idea, manuscript narrative, table preparation, figure creation, reference search and compilation were performed manually by authors. Various other statistical calculations were assisted by statistician.

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Publisher's note

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The appropriateness of initial intravenous empirical antibiotic consumption guided by digital antimicrobial stewardship tool: a correlation with the usage of antibiotics from the access and watch groups in ten Indonesian hospitals

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The appropriateness of initial intravenous empirical antibiotic consumption guided by digital antimicrobial stewardship tool: a correlation with the usage of antibiotics from the access and watch groups in ten Indonesian hospitals

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Background: RASPRO Indonesia Study Group for Antimicrobial Stewardship & Resistance has developed a digital antimicrobial stewardship (ASP) tool known as the e-RASPRO, which may provide a guideline for clinical decision on antibiotic prescribing for bacterial infection cases by integrating the WHO AWaRe (Access, Watch, Reserve) classification.

Methods: A multicenter retrospective correlational study was conducted using aggregated monthly hospital antibiotic prescribing data. A correlation test was conducted between the mean percentage on the appropriateness of initial intravenous empirical antibiotic consumption and the mean Defined Daily Dose (DDD) of antibiotics within a year (January to December 2024) in 10 Indonesian hospitals after the socialization of e-RASPRO tool between 2022 and 2024 in four major infections.

Results: There was a significant positive correlation between the mean of percentages on appropriateness of initial intravenous empirical antibiotic consumption in type I risk stratification guided by e-RASPRO tool and the mean DDD/100 patient-days of intravenous Penicillin as Access group antibiotic ($r = 0.598$, 95% CI: 0.021–0.873, $p = 0.041$) and a significant negative correlation with the mean DDD/100 patient-days of intravenous third-generation Cephalosporins as Watch group antibiotic ($r = -0.612$, 95% CI: −0.878 to −0.044, $p = 0.035$) after removed linear temporal trends.

Conclusion: Appropriateness of initial intravenous empirical antibiotic consumption in type I and II risk stratification guided by e-RASPRO tool was correlated with increased consumption of Penicillin as an Access group antibiotic and decreased consumption of third-generation cephalosporins as a Watch group antibiotic. This study did not describe a causal relationship between the use of the e-RASPRO tool and antibiotic consumption in the hospital.

KEYWORDS

antibiotic, appropriateness, defined daily dose, digital, empirical, intravenous, stewardship

1 Introduction

World Health Organization (WHO) has classified antibiotics into Access, Watch, and Reserve categories. It is expected that the target of antibiotic prescribing from the Access group in various countries may reach at least 60% (1, 2). Supports from hospital management, human resources and other supporting tools are absolutely necessary in order to achieve the WHO target. The implementation of the digital Antimicrobial Stewardship (ASP) may provide good results on the prescribing of antimicrobial agents and it may reduce Defined Daily Dose (DDD) of antibiotics; however, the appropriate digital model has yet to be determined (3–5). The WHO Access, Watch, Reserve (AWaRe) classification can be used as a guideline in consuming antimicrobial agents (6). Based on the current regulation in Indonesia, antibiotics from the Access category can be prescribed without any pre-authorization although appropriate indication would be necessary, while those from the Watch and Reserve groups must be given based on pre-authorization and supervision by the Antimicrobial Stewardship team, infection control consultants and the hospital's Antimicrobial Resistance Control Committee (ARCC) (7). On the other hand, the management and technology of antimicrobial prescribing, as well as the implementation and operational monitoring on the consumption of antimicrobial agents, are often overlooked a part of disparities in the development of National Action Plans (NAPs) (8).

A small-scale survey conducted in 2019, which involved 156 hospital respondents in Indonesia, found that 116 respondents reported that they had not implemented antimicrobial resistance control measures in their hospitals, largely due to the lack of a clear management framework for implementing such measures (9). Another larger survey conducted in Iran from 2022 to 2023 reported that 65% of antibiotics prescribed to inpatients belonged to the WHO Watch category (10). The RASPRO Indonesia Study Group for Antimicrobial Stewardship & Resistance views this as a gap in management, antimicrobial prescribing technology, as well as implementation and operational monitoring that could lead to the failure to implement the ASP in a hospital in Indonesia.

In order to narrow the gap, the RASPRO Indonesia Study Group for Antimicrobial Stewardship and Resistance has developed a Digital ASP tool known as the e-RASPRO, which features digital antibiotic guidelines that classify patients into Types I, II, and III risk stratification based on severity, immune status and medical history. The tool has also integrated the WHO AWaRe antibiotic classification by considering local microorganism pattern (if it is available at the hospital) as well as various considerations that have been evaluated through peer expert review at the hospital. By implementing the tool, it is expected that it can serve as one of modalities to provide a guideline for clinicians as well as monitoring, evaluating and reporting on the administration of prophylactic, empirical, and definitive antibiotics. The Digital ASP e-RASPRO tool can also facilitate on-site consultations between doctors, pharmacists and the hospital's ASP team, coordinate the conduct of prospective pre-authorization audits regarding antibiotic use in the hospital.

This study is expected to serve as a preliminary study involving multiple hospitals with a substantial volume of prescriptions. It aims to examine the correlation between the mean percentage of appropriate initial intravenous empirical antibiotic use, based on the Antibiotic Guidelines of the Digital Antimicrobial Stewardship Program (ASP) e-RASPRO tool for four major infections (intra-abdominal biliary infection, pneumonia, urinary tract infection, and skin and soft tissue infection), and the mean Defined Daily Dose (DDD) of intravenous antibiotics from the WHO Access and Watch categories in 2024 across 10 hospitals. We hypothesize that a higher rate of concordance with empirical prescribing guidelines for initial intravenous antibiotics in these four major infections will be associated with increased consumption of Access antibiotics and decreased consumption of Watch antibiotics. Nevertheless, we recognize that this study has not clearly explored the cause-and-effect relationship and remains limited to the use of initial intravenous empirical antibiotics, which is associated with antibiotic DDD within a year period of time.

2 Methods

2.1 Early socialization on implementing digital antimicrobial stewardship e-RASPRO tool

Socialization and training program on the Digital ASP e-RASPRO tool was conducted gradually by implementing the digital guidelines for empirical antibiotic therapy at 10 hospitals in Indonesia from 2022 to 2024. The Digital ASP e-RASPRO tool would guide clinicians in deciding on the administration of empirical antibiotics and help hospitals to monitor the appropriateness of the administered antibiotics whether it had been complied with current guidelines.

At these ten hospitals, the digital guidelines for empirical antibiotic therapy outlined in the Digital ASP e-RASPRO tool had been implemented, as agreed upon through peer expert

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reviews at each hospital. In this setting, patients with bacterial infection who would receive empirical antibiotics and would be admitted to an inpatient ward were divided into three risk stratification groups based on their disease severity, immune status, and medical history (5, 11):

- **Type I risk stratification group** is a group of patients with mild bacterial infection, whether immunocompetent or immunocompromised, whose infections do not meet the criteria for Type II or III risk stratification groups. In other words, they are at lower risk of infection with multidrug-resistant (MDR) bacteria.

  Based on the digital guidelines for empirical antibiotic therapy approved through peer expert review by each hospital, in the e-RASPRO tool, this group may receive empirical antibiotics from the Access category, such as Amoxicillin Clavulanate, Ampicillin Sulbactam (Penicillin class - Access) with or without a combination of Amikacin/Gentamicin (Aminoglycoside class - Access). In this risk stratification group, the Quinolone group, which falls under the Watch category, is used in cases of beta-lactam allergy or based on specific clinical considerations.
- **Type II risk stratification group** is a group of patients with mild bacterial infection with the following characteristics: (Immunocompromised AND/OR uncontrolled diabetes mellitus) + (history of antibiotic use within ≤ 90 days AND/OR history of hospitalization at a healthcare facility for 48 h or more (≥ 48 h) but less than 30 days ago (≤ 90 days) AND/OR history of medical device use within ≤ 90 days ago). The group of patients with such characteristics are at risk for infection by MDR bacteria—Extended-Spectrum Beta-Lactamases (ESBLs) (11–17). This group of patients may be prescribed anti-ESBL antibiotics from the Access - Watch category. Based on the digital guidelines for empirical antibiotic therapy approved through peer expert review by each hospital, in the e-RASPRO tool, this group may receive empiric antibiotic treatment of Carbapenem Sparing Agent in order to eradicate ESBLs involving the Access antibiotics, i.e., the combination of Ampicillin Sulbactam/Amoxicillin Clavulanate (Penicillin class - Access) must be combined with Amikacin/Gentamicin (Aminoglycoside class - Access). In this risk stratification group, the Quinolone group, which falls under the Watch category, is used in cases of beta-lactam allergy or based on specific clinical considerations.
- **Type III risk stratification group** is a group of patients with severe/threatening bacterial infection AND/OR patients with Healthcare Associated Infections (HAIs) AND/OR (Immunocompromised AND/OR uncontrolled diabetes mellitus) + (history of antibiotic use of ≤ 30 days ago AND/OR history of hospitalization at a healthcare facility for 48 h or more (≥ 48 h) but less than 30 days ago (≤ 30 days) AND/OR history of medical device use within ≤ 90 days ago). This group of patients with these characteristics is at high risk of mortality and is also at risk of infection by ESBL bacteria and other multidrug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant *Pseudomonas* spp., and others (11, 18–20). Based on the digital guidelines for empirical antibiotic therapy approved by peer experts at each hospital using the e-RASPRO tool, this group may receive antibiotics in the 'Watch' category, with or without combination therapy using antibiotics in the 'Access' category: Meropenem/Imipenem/Doripenem (Carbapenem class -Watch) with or without a combination of Amikacin/Gentamicin (Aminoglycoside class -Access). In cases of suspected MRSA infections, anti-MRSA antibiotics may be administered. The use of these antibiotics must undergo a pre-authorization process and prospective audit by the hospital's ASP Team. In this risk stratification group, Quinolone group, which falls under the 'Watch' category, are used in cases of carbapenem allergy or based on specific clinical considerations.

The Digital ASP e-RASPRO tool would notify doctors, pharmacists, and nurses regarding the category of antibiotics to be administered (Access, Watch, or Reserve). In accordance with national regulations in Indonesia, if the antibiotic to be used is categorized as Watch or Reserve, the pharmacy is required to consult with the hospital's ASP team, infection control consultant, and hospital ARUI for pre-authorization and prospective audit.

The Digital ASP e-RASPRO tool could be used to guide the selection of initial empirical antibiotics, guide subsequent changes or additions to empirical antibiotic therapy (if necessary), record definitive antibiotic therapy, guide the use of prophylactic antibiotics, issue notifications regarding prolonged antibiotic use, and provide physician notes for difficult-to-treat bacterial infection cases requiring comprehensive discussion. However, in the flowchart below, we have limited the scope to the system that guides physicians in determining the use of initial empirical antibiotics.

The following is a screenshot from the Digital ASP e-RASPRO tool showing the workflow for determining the use of initial empirical antibiotics (the first empirical antibiotics prescribed by a doctor when a patient is admitted to the hospital), using the digital empirical antibiotic guidelines on this device (5).

The Digital ASP e-RASPRO tool is designed to guide and monitor physicians in prescribing antibiotics. Figure 1 shows boxes that can be selected by physicians for antibiotic use in daily practice for hospitalized patients. Box (A) was referred to as the RASAL Box. This box must be checked when the doctor decided to administer initial empirical antibiotics (intravenous or oral). The initial empirical antibiotic was the first antibiotic decided by the doctor to administer for a patient upon admission to the inpatient ward. Box (B) was referred to as the RASLAN Box. This box must be checked when the doctor decided to change the empirical antibiotic regimen during treatment, if necessary. The RASLAN box could be used as a guide for escalating (step-up) or de-escalating (step down) antibiotic treatment based on digital empirical guidelines and the doctor's clinical observations.

Box (C) was referred to as the RASPRAIA Box. This box must be checked and filled out when a doctor decided that there were specific indications requiring prolonged antibiotic administration (whether empirical or definitive). If antibiotic use exceeds a

certain duration and the doctor failed to check the RASPRAJA Box, the hospital may issue an Automatic Stop Order (ASO).

Box (D) was called the RASPATUR Box. This box must be checked when a doctor prescribed a definitive antibiotic. Box (E) was called the RASGRASI Box. This box can be checked when a doctor would report difficult-to-treat bacterial infection cases, in which the patient had already received multiple changes of antibiotic treatment. When the RASGRASI Box was clicked, a notification would be sent to the pharmacist, and the difficult case could be submitted for a collaborative case review involving the Hospital's ARUC. Box (F) was called the e-Prophylaxis Box, which could be used to guide doctors in the administering prophylactic antibiotics.

After the doctor clicked the RASAL box (A) in Figure 1, the screen advanced to the next phase, as shown in Figure 2. Figure 2 illustrates how the Digital ASP e-RASPRO tool guided the physician in administering initial empirical antibiotics (intravenous or oral) when a patient was admitted to the hospital.

The doctor could input data about the patient's condition based on current clinical observations, including: (1) Severity of illness of the patient's infectious disease (Sepsis/Non-Sepsis, Febrile Neutropenia/Healthcare-Associated Infections/Life-Threatening Organ Perforation/Encephalopathy associated with severe bacterial infection). (2) Immune status (immunocompetent/immunocompromised). (3) The patient's medical history over the past 30 or 90 days (history of antibiotic consumption, history of hospitalisation, and history of medical device use). the Digital ASP e-RASPRO tool would provide doctors with information regarding patient risk stratification in accordance with the various academic citations previously cited (G).

After that, the doctor could continue this workflow by clicking on the patient's site of bacterial infection (H). The digital empirical antibiotic guide would provide initial empirical antibiotic options that could be administered to the patient based on the patient's risk stratification. The empirical antibiotic guide was customized according to the guideline that had been agreed upon through a peer expert review at each hospital (I). The doctor could then select the initial empirical antibiotic, along with the dosage, frequency of administration, and route of administration. Through this screen, the doctor would also immediately receive information on whether the prescribed antibiotic fell under the Access, Watch, or Reserve category (J).

After the doctor submitted the initial empirical antibiotic prescription as shown in Figure 2, the workflow in this system would forward it to the pharmacist for review.

Figure 3 shows the pharmacist's screen, which was used to review the prescribed antibiotics. Through this screen, the pharmacist would be informed of various details, including: (1) Site of infection, (2) Patient risk stratification, (3) Appropriateness of antibiotic prescription based on the digital empirical guidelines (by clicking the 'Guide' button). (4) Type of antibiotic that had been administered: antibiotic category (Access/Watch/Reserve). (5) Dose, frequency and route of administration.

Pharmacists could click the phone icon in the upper-right corner to consult with the hospital's ASP Team on-site if the prescribed antibiotics did not comply with the guidelines AND/OR if the prescribed antibiotics fell under the Watch or Reserve categories. If no agreement had been reached regarding the use of antibiotics among the pharmacist, the hospital's ASP team, and the physician, but the antibiotics must be dispensed immediately for patient safety reasons, the pharmacist may issue a special notification through this system. These notifications could then be submitted to hospital management every three to six months (semester) to serve as a basis for evaluation and to determine future policies regarding the prudent use of antibiotics.


e-RASAL
(I)
(II)
(J)
(J)

Once the pharmacist had completed the assessment of the initial empirical antibiotic prescription as shown in Figure 3, the pharmacist could submit the assessment and the workflow on the system would forward it to the nurse so that they could also monitor antibiotic use.

Figure 4 shows the nurse's screen, in which the nurse could access various pieces of information, namely: (1) the site of the patient's infection, (2) the patient's risk stratification, (3) the appropriateness of antibiotic prescription according to the digital empirical guidelines (by clicking the 'Guide' button), (4) the type of antibiotic that had been administered and the antibiotic category (Access/Watch/Reserve), (5) The dose, frequency and route of administration of antibiotics. Nurses and pharmacists could also monitor how many days the antibiotics were administered. If a doctor prescribed long-term antibiotics, the nurse and/or pharmacist could remind the doctor to document the indication for long-term antibiotic use in the RASPRAJA Box (Figure 1F), because if the indication had not been clearly documented through this box, the hospital might enforce Automatic Stop Order (ASO).

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2.2 Obtaining and analyzing data

This was a multicenter retrospective correlational study using aggregated monthly hospital antibiotic prescribing data. The data were retrospectively collected from inpatient units at 10 hospitals between January and December 2024 using the Digital Antimicrobial Stewardship Program (ASP) e-RASPRO tool. The inclusion criteria comprised initial intravenous empirical antibiotics prescribed for all inpatients, both adult and pediatric, including ICU patients, for four major infections. The use of empirical combination therapy initiation was included in the calculation and was declared appropriate if the combination therapy was in accordance with the antibiotic guidelines in e-RASPRO. In accordance with the study title and primary objective, change of antibiotic from the initial antibiotic or a change of antibiotic to the definitive antibiotic that occurred during hospitalization were excluded. The same empirical antibiotic guideline was in effect at all 10 hospitals, as agreed upon by each hospital's peer expert review committee. Data were retrieved in early 2025, which included the following:

1. Percentage of Appropriate Use of Initial Empirical Intravenous Antibiotics (the first empirical intravenous antibiotic administered upon a patient's admission to the inpatient ward) for the four most common infections (the 'Big Four' infections), i.e., Intubation Infections, Pneumonia, Urinary Tract Infection and Pyelonephritis, and Soft Tissue Infection at 10 hospitals between January and December 2024.

The four major infections selected were those that deemed to be highly prevalent in the 10 hospitals, which had been studied during 2024. The consumption of a single initial intravenous empirical antibiotic was categorized as appropriate if it complied with the guidelines in the Digital ASP e-RASPRO tool. The use of a combination of initial intravenous empirical antibiotics was categorized as appropriate if both complied with the guideline in the Digital ASP e-RASPRO tool.

(1) Mean DDD of Intravenous Antibiotics. In accordance with Indonesian national regulations, DDD refers to the Defined Daily Dose/100 patient-days, hereafter termed DDD. DDD / 100 *patient days* =

$$\frac{\text{Total Antibiotic Used (grams)} \div \text{WHO DDD}}{\text{Total Length of Stay (LOS)}} \times 100.$$

Data about mean DDD for the five largest classes of intravenous antibiotics were collected and calculated from 10 hospitals, specifically for the Access Group (Penicillins and Aminoglycosides) and the Watch Group (third-generation Cephalosporins, Quinolone, and Carbapenem group) between January and December 2024 to observe the trends of antibiotic consumption during that year.

Afterwards, the percentage on the appropriateness of initial intravenous empirical antibiotic consumption based on the digital antibiotic guidelines was described according to patient risk stratification groups for the 4 major infections, as well as the mean DDD of the five classes intravenous antibiotics between the 1st semester (January to June 2024) and 2nd semester (July to December 2024) during the implementation of the Digital ASP e-RASPRO tool. A correlation analysis was conducted between the mean percentage on the appropriateness of initial empirical intravenous antibiotic consumption based on the digital antibiotic guidelines for the 4 major infections and the mean DDD of intravenous antibiotics in 2024.

All patient-level identifiers were removed and anonymized before aggregation and analysis were performed. Data processing, discussions, and various verifications were conducted from mid- to late 2025. The appropriateness of initial intravenous empirical antibiotics consumption and the DDD of intravenous antibiotics were verified by pharmacists from each hospital using the Digital ASP e-RASPRO tool. All data extracted from the Digital ASP e-RASPRO tool was then re-verified by the ASOC and peer experts from the ten hospitals. Data analysis and manuscript writing began in early 2026 under the supervision of the various parties involved in this study.

3 Results

The results of this study are presented in the five tables provided by the researchers. All data were obtained in 2024 from 10 hospitals.

Table 1 shows the total number of initial empirical intravenous antibiotic prescriptions for the four major infections at 10 hospitals which was recorded in the Digital ASP e-RASPRO tool, which reached 20,907 prescriptions during 2024. During the first semester, about 4,866 prescriptions were documented, while in the second semester, 16,041 prescriptions were recorded. There was an increase in the mean percentage on the appropriateness of initial intravenous empirical antibiotic consumption in the combined type I and II risk stratification group from 65.1% in the first semester to 98.6% in the second semester; while for those in the type III risk stratification group, there was an increase from 0.58% in the first semester to 86.2% in the second semester.

Table 2 shows a sharp increase in the mean DDD for Penicillin-class antibiotics and a decrease for third-generation Cephalosporins. The DDD for Penicillin-class antibiotics increased from 30.618 (7.245) to 47.679 (7.574), while the DDD for intravenous third-generation Cephalosporins consumption decreased from 16.369 in the first semester to 15.071 in the second semester. There was an increase in DDD for aminoglycosides, Quinolone and Carbapenem, but it was not as significant as the increase in DDD for Penicillin.

Table 3 shows a significant correlation between the appropriateness of initial intravenous empirical antibiotic consumption in type I and II risk stratification with the use of intravenous penicillin and third-generation Cephalosporins. After detrending via standardized residuals to remove linear temporal trends, significant positive and negative correlations persisted between the mean percentage on appropriate initial intravenous empirical antibiotics in the combined type I and II risk stratification group and the mean DDD of intravenous Penicillin ($r = 0.598$, 95% CI [0.021–0.873], $p = 0.041$) and intravenous third-generation Cephalosporin ($r = -0.652$, 95% CI [−0.876 to −0.044], $p = 0.035$). For both antibiotics, the 95% confidence intervals for raw and detrended analyses excluded zero, indicating that month-to-month changes in

TABLE 2 Description on mean percentage of appropriateness of initial intravenous empirical antibiotic consumption in two groups (combined type I and II risk stratification group and type III group) based on the digital ASP e-RASPRO tool guidelines for the four major infectious diseases (first and second semesters in 2024) at 10 hospitals.

Initial intravenous empirical antibiotics for the four major infections	The 1st semester January to June 2024		The 2nd semester July to December 2024		Total
	n	Mean Percentage of Appropriateness (x100%)	n	Mean Percentage of Appropriateness (x100%)	
Total Prescription	6,980		10,821		38,937
Type I + II Risk Stratification		0.833 (0.765)		0.966 (0.063)	–
Type III Risk Stratification		0.828 (0.295)		0.833 (0.860)	–

Values in parentheses are standard deviations.

TABLE 3 Mean quantity of the intravenous antibiotics in the first and second semesters in the digital ASP e-RASPRO tool guidelines implementation hospitals in 2024 at 10 hospitals.

Antibiotic class	The 1st semester January to June 2024 Mean DDD	The 2nd semester July to December 2024 Mean DDD
Penicillin	30.648 (7.213)	42.979 (7.371)
Anti-staphylococcal	9.107 (5.283)	9.996 (5.322)
Third-generation Cephalosporins	16.569 (3.961)	13.191 (3.193)
Quinolone	12.995 (2.961)	11.706 (3.401)
Carbapenem	6.456 (1.985)	8.619 (2.394)

Values in parentheses are standard deviations.

appropriateness were associated with concurrent changes in antibiotic use independent of overall secular trends.

No significant correlation was found between the mean percentage on appropriate initial intravenous empirical antibiotics in the combined type I and II risk stratification group and the mean DDD of intravenous Quinolone, even though the Quinolone group was used as an alternative antibiotic for this group.

Table 4 shows an insignificant correlation between the variables tested. After detrending via standardized residuals to remove linear temporal trends, correlations between the mean percentage on appropriate initial intravenous empirical antibiotics in the type III risk stratification group and the mean DDD of intravenous remained non-significant close to zero for both intravenous Quinolone ($r = 0.001$, 95% CI −0.576–0.572; $p = 0.825$) and Carbapenem ($r = -0.177$, 95% CI −0.722–0.569; $p = 0.625$).

Table 5 shows various correlations between appropriateness on initial empirical intravenous antibiotic consumption and DDD of antibiotics in four major infections grouped by risk stratification. In type I + II risk stratification patients, prescribing appropriateness was significantly positively correlated with intravenous Penicillin consumption for pneumonia ($n = 12$; $r = 0.785$, 95% CI 0.377–0.938; $p = 0.002$), urinary tract infection and pyelonephritis ($n = 10$; $r = 0.858$, 95% CI 0.416–0.913; $p = 0.140$), and soft tissue infection ($n = 11$; $r = 0.625$, 95% CI 0.052–0.888, $p = 0.041$). Significant inverse correlations with Watch group antibiotics were observed for intravenous third-generation Cephalosporins in pneumonia ($n = 12$; $r = -0.719$, 95% CI −0.915 to −0.2 $p = 0.008$), urinary tract infection and pyelonephritis ($n = 10$; $r = -0.783$, 95% CI −0.940 to −0.316; $p = 0.007$), and soft tissue infection ($n = 11$; $r = -0.760$, 95% CI −0.935 to −0.34 $p = 0.007$), and for Carbapenem in intrabdominal infection ($n = 9$; $r = -0.684$, 95% CI −0.932 to −0.171; $p = 0.456$).

4 Discussion

The issue of the widespread use of third-generation Cephalosporins in Indonesia has been highlighted in a previous study (29). Other studies in Thailand and Cameroon have also highlighted the issue of third-generation Cephalosporins consumption being the most commonly prescribed antibiotics (30, 31). This might be due to physician's limited knowledge regarding antibiotics, inadequate laboratory facilities and poor institutional policies (31).

The WHO has documented that the third-generation Cephalosporins fall under the Watch group. Meanwhile, as has been explained earlier, WHO has set a target for prescribing antibiotic from the Access category as much as ≥60% of total antibiotic prescriptions. It is expected that the utilization of digital ASP tool may improve institutional policies for monitoring appropriate antibiotic consumption in hospitals. The digital ASP e-RASPRO tool has been implemented at the 10 hospitals since 2022.

Table 1 shows increased prescribing of initial empirical intravenous antibiotics that has been documented on the Digital e-RASPRO tool. This may be due to several factors, such as an increase in the number of patients or improved compliance with the utilization of Digital ASP e-RASPRO tool that may lead to more physicians entering data into this digital device as a result of socialization efforts regarding its use that have been conducted in previous years. Table 1 also shows that the mean percentage on the appropriateness of initial intravenous empirical antibiotic consumption that had been increased from the first semester to the second semester. It is followed by Table 2, which illustrates a sharp increase in mean DDD of intravenous Penicillin-class antibiotics categorized as Access and a decrease in mean DDD of intravenous third-generation Cephalosporin-class antibiotics categorized as Watch group. It appears that there is a shift in the trend here. This may also be

TABLE 3 [illegible]

Months	Appropriateness (x100%)		Access				Watch					
			Penicillin		Aminoglycoside		Third-generation Cephalosporins		Quinolone		Carbapenem	
			Mean DDD		Mean DDD		Mean DDD		Mean DDD		Mean DDD	
		r		0.781		0.223		−0.749		−0.159		−0.077
		95% CI[a]		0.376 to 0.938		−0.402 to 0.704		−0.923 to −0.307		−0.668 to 0.451		−0.618 to 0.512
		p		0.003		0.490		0.005		0.621		0.811
		Detrended r		0.598		0.144		−0.612		−0.283		−0.182
		95% CI Detrended r		0.020 to 0.873		−0.489 to 0.689		−0.878 to −0.014		−0.750 to 0.336		−0.691 to 0.455
		Detrended p		0.041		0.656		0.035		0.372		0.751
January	0.3467		12.99		8.80		19.96		33.52		7.83	
February	0.2727		22.24		9.81		16.60		36.17		9.89	
March	0.3455		27.41		9.92		16.42		27.73		4.87	
April	0.8265		33.26		10.18		13.27		23.83		8.83	
May	0.9947		37.84		9.41		11.97		17.86		6.71	
June	0.9394		41.86		10.42		11.94		24.47		4.49	
July	0.8887		40.75		10.29		13.09		32.03		8.11	
August	0.9152		43.90		12.03		14.42		74.21		10.79	
September	0.9329		47.34		10.18		14.38		29.91		10.83	
October	0.8862		48.39		10.97		11.89		53.61		10.83	
November	0.8963		48.33		7.43		12.87		31.75		10.39	
December	0.8864		61.95		8.25		11.56		56.65		8.83	

r, Pearson correlation coefficient; CI, confidence interval; p, two-tailed nominal p-value. [illegible] Number of monthly observations analysed, with DDD = 12 months. [illegible]

[a][illegible]

Table 3 Descriptive and correlation (Pearson correlation coefficient) between the appropriateness of Antibiotic prescription in type II risk stratification group based on the Antibiotic guidelines of the Digital ASPEK-RASPRO tool for the four major infectious diseases with the mean DOD of intravenous quinolone and carbapenem in 2019 in 20 hospitals.

Months	Appropriateness (x100%)		Watch	
			Quinolone	Carbapenem
			Mean DDD	Mean DDD
		r		0.139	−0.111
		95% CI		−0.344 to 0.498	−0.740 to 0.498
		P		0.724	0.557
		Detrended r*		0.081	−0.377
		95% CI Detrended r*		−0.230 to 0.472	−0.721 to 0.567
		Detrended p*		0.826	0.429
January			31.52		7.85
February	0.2389		30.17		9.49
March			27.75		4.81
April	0.7455		25.65		5.85
May	0.6388		27.06		6.21
June	0.6811		21.47		4.49
July	0.9536		31.03		5.11
August	0.9428		31.24		10.73
September	0.8284		25.91		10.15
October	0.8479		31.66		10.43
November	0.8754		31.75		10.31
December	0.9368		30.66		3.99

*Partial correlation coefficient, CI, confidence interval, p, two-sided numerical p-value 95% CI calculated via Fisher Z transformation [...] ln((1+r)/(1−r))/2 with r = 0.139, 95%CI for Z = 0.2 ± 1.96 × 1/36, back-transformed to r. Computed using: SPSS v26 CURVEFIT /VARIABLES=DOD WITH LITOUTPATIENT /INDEPENDENT=TIME /CONSTANT /MODEL=LINEAR. Detrended r = Pearson correlation of standardized residuals (ZRESID) from separate linear regressions of each variable on sequential month (1–12). SPSS v26 REGRESSION /DEPENDENT ZRESID /METHOD=ENTER. Confidence intervals were based on monthly aggregate observations, not individual prescriptions. Missing data for January and March was due to administrative issues during data sorting, which suggested a lack of data parity. Therefore, it was decided to exclude data for these months. Numbers of monthly observations consistent with DDD > 30 months. No adjustments for multiple comparisons were applied. All analyses are exploratory.

Analysis by individual hospitals with data input and analysis were verified by the authors supported by statistician.

due to the socialization or awareness campaign regarding the utilization of the tool that have been conducted in previous years that are associated with the WHO AWaRe initiatives.

The shift in prescribing trends toward antibiotics in the Access group (intravenous Penicillin) appears to be gaining momentum however, there has also been increased consumption in other antibiotics classified as the Watch group, namely the intravenous Quinolone and Carbapenem classes. Regarding the increased antibiotic consumption, intravenous Quinolone and Carbapenem should be considered along with other biases such as increased number of patients in the 2nd semester, an increase in the number of patients classified as type II risk stratification group, or an increase in the number of patients with infections who are excluded from those with the four major infections, as well as an increase in the number of physicians prescribing intravenous Quinolones as an alternative antibiotic across all three stratification groups.

According to the antibiotic guideline in the Digital ASPEK-RASPRO tool developed for the 10 hospitals, antibiotics from the Access group of the Penicillin class – such as Ampicillin Sulbactam and Amoxicillin Clavulanate in combination with Antibiotics of Gentamicin—are indeed designated as antibiotics of choice for patients in type I and II risk stratification groups. A previous study conducted at three hospitals in Indonesia found that more than 80% of patients fell into type I risk stratification group (32). The same pattern holds true in this study, it could still influence a shift in antibiotic prescribing trends, particularly from the Watch Category to the Access Category.

According to the antibiotic guideline in the Digital ASPEK-RASPRO tool, patients classified in the type I risk stratification group are empirically recommended to receive antibiotics from the Penicillin class (Ampicillin-Sulbactam or Amoxicillin-Clavulanate) with or without a combination of Aminoglycoside, namely Antibiotic or Gentamicin. The intravenous third-generation Cephalosporins have been intentionally excluded from the list of antibiotics for patients in the type I risk stratification group in order to prevent a surge in prescriptions for intravenous third-generation Cephalosporins, which are classified as Watch Category antibiotics.

For the type II risk stratification group, empirical treatment guidelines recommend administering antibiotics from the Access Category of the Penicillin Class—specifically Ampicillin Sulbactam or Amoxicillin Clavulanate – which must be used in combination with an Aminoglycoside, such as Antibiotic or Gentamicin. This combination is used as a Carbapenem Sparing Agent, as agreed upon by peer experts from the ten hospitals, to treat patient groups at higher risk of ESBL infections.

TABLE 6 The correlation between the [illegible]

Types of Infection	Appropriateness	n	Penicillins r	Penicillins 95% CI[a]	Penicillins p	Aminoglycosides r	Aminoglycosides 95% CI[a]	Aminoglycosides p	First-generation Cephalosporins r	First-generation Cephalosporins 95% CI[a]	First-generation Cephalosporins p	Quinolones r	Quinolones 95% CI[a]	Quinolones p	Carbapenems r	Carbapenems 95% CI[a]	Carbapenems p
Respiratory Infection	Type I + II Risk Stratification	[illegible]	0.436	−0.533 to 0.882	0.950	−0.106	−0.704 to 0.485	0.807	0.011	−0.594 to 0.605	0.957	−0.600	−0.928 to 0.021	0.038	−0.899	−0.933 to −0.071	0.020
	Type III Risk Stratification	8										0.600	−0.144 to 0.921	0.116	0.611	−0.080 to 0.722	0.060
Pneumonia	Type I + II Risk Stratification	11	0.780	0.177 to 0.938	0.013	0.130	−0.449 to 0.609	0.001	−0.759	−0.931 to −0.255	0.008	−0.180	−0.637 to 0.487	0.730	−0.026	−0.549 to 0.535	0.936
	Type III Risk Stratification	10										0.166	−0.517 to 0.714	0.647	−0.305	−0.756 to 0.361	0.608
Urinary Tract Infection and Pyelonephritis	Type I + II Risk Stratification	10	0.654	0.018 to 0.913	0.040	0.369	−0.553 to 0.606	0.297	−0.701	−0.809 to −0.116	0.007	−0.582	−0.777 to 0.098	0.086	−0.041	−0.654 to 0.596	0.862
	Type III Risk Stratification	8										−0.223	−0.793 to 0.562	0.603	−0.479	−0.888 to 0.330	0.230
Soft Tissue Infection (Skin)/Joint Bone/Abscess Rupture	Type I + II Risk Stratification	11	0.622	0.052 to 0.888	0.041	0.044	−0.133 to 0.752	0.380	−0.701	−0.921 to −0.359	0.007	−0.296	−0.761 to 0.368	0.377	−0.057	−0.633 to 0.561	0.877
	Type III Risk Stratification	9										0.237	−0.504 to 0.778	0.514	−0.081	−0.702 to 0.605	0.824

r, Pearson correlation coefficient; CI, confidence interval; p, two-tailed p-value. [illegible] No adjustment for multiple comparisons was applied. All analyses are exploratory.

[a] [illegible]

The agreed-upon antibiotic guidelines in the Digital ASP e-RASPRO tool has suggested that Carbapenem antibiotics should not be used empirically for patients in the 'type II risk stratification group (patients at risk for ESBL infections), with the aim of preventing a surge in empirical carbapenem prescriptions in daily practice.

Meanwhile, the Quinolone class antibiotic is still considered appropriate to be used as an alternative empirical treatment in all risk stratification groups, particularly in case of beta-lactam allergy or based on other clinical considerations. Since the same empirical antibiotics are used in both risk stratification groups, in Table 3 we have combined type I and II risk stratification group and correlated them with the mean DDD of each antibiotic class.

Table 3 The persistence of significant bivariate correlations between the mean percentage on appropriate initial intravenous empirical antibiotics in the combined type I and II risk stratification group and the mean DDD of intravenous Penicillin ($r = 0.398$, 95% CI 0.321–0.872; $p = 0.041$) and intravenous third-generation Cephalosporins ($r = -0.461$; 95% CI −0.678 to −0.046; $p = 0.035$) provides robust evidence that e-RASPRO implementation is correlated with trend shifting from Watch to Access antibiotics beyond general time trends. The consistency of significant associations before and after forecasting, with confidence intervals excluding trivial effects, indicates that e-RASPRO is associated with meaningful shifts toward WHO AWaRe aligned prescribing behaviour. Patient-level interrupted time-series analyses are warranted to confirm individual-level mechanisms. This study did not calculate the number of patients in each of the risk stratification groups (type I, II, and III); however, a previous study conducted at three hospitals in Slovenia using the Digital ASP e-RASPRO tool suggests that the number of patients in type I risk stratification group was significantly higher than those in type II and III risk stratification groups [32]. If the same pattern occurs in this study, then the appropriateness of early intravenous empirical antibiotic consumption in type I risk stratification group will likely to have a greater influence on the correlation of the mean DDD of intravenous Penicillin with third-generation Cephalosporins antibiotics compared to those in type II risk stratification group.

The lack of a significant positive correlation between the mean percentage on the appropriateness of initial intravenous empirical antibiotic consumption in the combined type I and II risk stratification group for the four major infections and the mean DDD of Aminoglycoside antibiotics ($r = 0.184$, 95% CI −0.459–0.695; $p = 0.568$) may exist due to the fact that Aminoglycoside antibiotics has not been the preferred antibiotic of choice for physicians in daily clinical practice compared to penicillin antibiotics. In addition, Quinolone and Carbapenem are classified as Watch group antibiotics, in which a significant negative correlation is also expected. The Quinolone class can still be considered empirically appropriate for patients in type I and II risk stratification groups, however, its role has been marginalized as alternative antibiotic treatment.

The absence of a significant negative correlation between the mean percentage on the appropriateness of early intravenous empirical antibiotic consumption in the combined type I and II risk stratification group for the four major infections and the mean DDD of intravenous Quinolone antibiotics may be due to the fact that some physicians still consider prescribing intravenous Quinolone antibiotics as an alternative for patients classified in the combined type I and II risk stratification group based on specific clinical considerations, which can actually still be considered appropriate for them. However, the likelihood of using antibiotics from the intravenous Quinolone class here is not as high as that of those the intravenous Penicillin class. These findings may also indicate that the Penicillin class is the preferred class of antibiotics compared to the Quinolone class.

The consumption of intravenous Quinolone antibiotics for patients in type III risk stratification group, as well as the frequent switching of empirical antibiotic treatment or the switch into definitive antibiotic treatment using antibiotics from Quinolone class, may also be considered as potential causes that warrant further investigation. It may affect the mean DDD of quinolone antibiotics and influence the correlation among variables. Another possible reason for these results is the high number of cases of infections other than the 'major four' that are treated with Quinolone. Indonesia is a tropical country with many cases of typhoid fever or salmonellosis, for which the quinolone class is known as the primary empirical antibiotic of choice. These factors should be considered as potential influences on the mean DDD of Quinolone antibiotics.

The absence of a significant negative correlation between the mean percentage on the appropriateness of initial intravenous empirical antibiotic consumption in the combined type I and II risk stratification group for the four major infections and the mean DDD of Carbapenem-class antibiotics may also be influenced by the empirical carbapenem-class antibiotics consumption for patients in type III risk stratification group or other factors. Other reasons also need to be considered, such as the large number of clinicians prescribing carbapenem antibiotics based on culture results. However, more comprehensive research is needed to understand this more clearly.

Table 4 describes the correlation between the mean percentage on the appropriateness initial intravenous empirical antibiotic consumption in type III risk stratification group for the four major infections and the mean DDD of intravenous Quinolone and Carbapenem antibiotics. As previously explained, Carbapenem-class antibiotics, with or without combination therapy with Aminoglycoside-class antibiotics, are the recommended intravenous empirical antibiotic treatment in antibiotic guidelines mentioned the Digital ASP e-RASPRO tool for patients in the type III risk stratification group. Meanwhile, Quinolone-class antibiotics are used as alternative empirical antibiotic treatment in cases of Carbapenem allergy or based on other clinical considerations. Actually, these findings do not indicate a significant positive correlation between the appropriateness of initial intravenous empirical antibiotic consumption in type III risk stratification group for the four major infections and the mean DDD of intravenous Quinolone ($r = 0.081$, 95% CI −0.573–0.672; $p = 0.825$) and Carbapenem ($r = -0.177$, 95% CI −0.722–0.507; $p = 0.625$).

The utilization of Quinolone-class antibiotics in this group is still considered appropriate, even though Quinolone are considered as alternative antibiotics in this risk stratification group. Various analyses of other possibilities also need to be conducted, such as the potential use of quinolones in type I and

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II risk stratification groups as alternative antibiotic treatment or other factors that could affect the mean DDD of intravenous Quinolone.

A previous study using the Digital ASP e-RASPRO tool at three hospitals in Indonesia over a three-month period has shown that only about 14% of patients fall into type III risk stratification group IB (20). If this were also the case in this study, then the number of patients requiring carbapenem-class antibiotics as initial empirical intravenous treatment would actually be quite small. This could certainly be a factor that may affect mean DDD of Carbapenem-class antibiotics. However, this certainly requires further research. However, it turns out that no significant correlation was found between the mean percentage on the appropriateness initial intravenous empirical antibiotic consumption in type III risk stratification group for the four major infections and the mean DDD of intravenous Quinolone and Carbapenem antibiotics, although the recommended antibiotic in this group of risk stratification is Carbapenem.

Table 5 provides robust statistical evidence that e-RASPRO implementation was correlated with shifting from Watch to Access antibiotics in infections where the shifting is guideline-concordant. The significant inverse correlation between the mean percentage on appropriate initial intravenous empirical antibiotics in the type I and II risk stratification group and the mean DDD of intravenous Carbapenem for intrabiliary infection ($n = 9$; $r_s = -0.899$, 95% CI: −0.983 to −0.101; $p = 0.006$) reflects baseline empiric carbapenem use for type I and II risk stratification for intrabiliary infection was successfully de-escalated post e-RASPRO tool guidance.

In contrast, the mean percentage on the appropriateness of initial intravenous empirical antibiotics in the combined type I and II risk stratification group for intrabiliary infection was not correlated with the mean DOD of intravenous Penicillin and intravenous third-generation Cephalosporins. In this regard, various possibilities should be evaluated further.

In the pneumonia, urinary tract infection and pyelonephritis and soft tissue infection groups, there was a similar pattern to that described in Table 5. The results showed a significant positive correlation between suitability in type I and II risk stratification with DDD intravenous Penicillin and a significant negative correlation between suitability in type I and II risk stratification with DDD intravenous third-generation Cephalosporins.

In this manuscript, the DDD results may reflect broader hospital antibiotic use, including definitive therapy, subsequent antibiotic changes, and infections outside the four selected infection groups. This means the findings should remain exploratory and non-causal. Further investigation is also necessary regarding how many cases that need continuation of initial intravenous empirical antibiotic treatment to achieve patient recovery, or the treatment should be continued based on culture results, which would indicate that the initial intravenous empirical antibiotics administered are indeed effective in treating the patient. Certainly, such factors may also explain the correlation between the appropriateness of initial intravenous empirical antibiotic consumption and the mean DDD of antibiotics. This study does not control for several confounding factors, including patient volume, risk stratification distribution, case mix of infections, and infections other than the four major infections. Results must be interpreted cautiously. The analysis utilized 12-month aggregated data per infection type, and the potential for temporal confounding within each subgroup cannot be excluded, as demonstrated in the overall time-series sensitivity analysis. Therefore, these correlations should be considered hypothesis-generating rather than confirmatory of a causal relationship between e-RASPRO-guided appropriateness and antibiotic consumption patterns. Further research using more comprehensive methods is needed to establish causal relationships.

However, with these preliminary results, it is hoped that the utilization of the Digital ASP e-RASPRO tool can be an innovation in order antimicrobial stewardship program. Digital health technologies that can optimize the consumption of antimicrobial agents and can minimize the impact of healthcare on antimicrobial resistance have the potential to support development and utilization of high-quality data, which are highly beneficial for clinical management and improvement of decision-making (39).

5 Conclusion

Use of the e-RASPRO as a digital antimicrobial stewardship tool was correlated with increased intravenous Penicillin consumption and decreased third-generation Cephalosporin consumption. For patients stratified as risk types I and II compliance was significantly correlated positively with intravenous Penicillin DDD and negatively with intravenous third-generation Cephalosporin DDD in pneumonia, urinary tract infections and pyelonephritis, and soft tissue infections. Further research using more comprehensive methods is needed to establish a causal relationship.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Research Ethics of Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia, *Reference Number* 026/KER/FK/02/2023. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

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Author contributions

RN: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. WL: Data curation, Formal analysis, Project administration, Supervision, Writing – review & editing. TM: Data curation, Project administration, Resources, Writing – review & editing. HA: Data curation, Investigation, Writing – review & editing. AA: Investigation, Project administration, Writing – review & editing. SM: Resources, Supervision, Writing – review & editing. SR: Resources, Supervision, Writing – review & editing. HA: Data curation, Software, Writing – review & editing. YS: Supervision, Writing – review & editing. MF: Supervision, Writing – review & editing. IS: Supervision, Writing – review & editing.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in some statistical calculations in this manuscript (as noted in several tables) due to software deficiencies. All data input, analysis, and conclusions were verified by authors and with the assistance of a statistician. The research idea, manuscript narrative, table preparation, figure creation, reference search and compilation were performed manually by authors. Various other statistical calculations were assisted by statistician.

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