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Faculty of Pharmacy

Department of Clinical Pharmacy

Summary of the Ph.D. Thesis

CERTAIN ASPECTS OF PHARMACIST CONTRIBUTION AND DIFFERENT WAYS OF COMBATTING INFECTIOUS DISEASES

Ikhwan Yuda Kusuma

Supervisors:

Dr. Ria Benkő, PhD
Dr. Mária Matuz, PhD

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University of Szeged

Doctoral School of Pharmaceutical Sciences

Institute of Clinical Pharmacy

Programme director: **Prof. Dr. Deszö Csupor**

Department of Clinical Pharmacy

Supervisors: **Dr. Ria Benkő, PhD** and **Dr. Mária Matuz, PhD Ikhwan Yuda Kusuma**

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1. INTRODUCTION

Infectious diseases remain a global health threat, especially in low- and middle-income countries (LMICs), where diagnostic limitations and unequal healthcare access persist. The COVID-19 pandemic exposed weaknesses in health systems and highlighted the crucial role of antimicrobials. However, antimicrobial resistance (AMR), driven by inappropriate use, poses a growing threat, linked to nearly 5 million deaths globally in 2019. Pharmacists play an essential role in antimicrobial stewardship (AMS) through drug utilization research (DUR), education, and infection control. The pandemic also accelerated digital health, including telepharmacy, which offers remote pharmaceutical care but faces barriers in implementation, particularly in LMICs. This thesis investigates four pharmacist-driven strategies to combat infectious diseases, focusing on antibiotic use in the elderly, pharmacy education, antiviral effectiveness, and telepharmacy readiness.

1.1 Rationale for Study I: Antibiotic Use in the Elderly in Ambulatory Care

The elderly population in Europe is increasing, with individuals aged ≥65 years comprising nearly 30% of the adult population in Hungary and Sweden in 2019, and projected to rise further by 2030. Aging is linked to immunosenescence, resulting in higher infection risk. However, data on antibiotic use among the elderly in outpatient settings remain limited, as most studies focus on institutional care. This study addresses this gap through a cross-national analysis of ambulatory antibiotic use in Hungary and Sweden.

1.2 Rationale for Study II: AMR Knowledge Assessment in Pharmacy Students

Pharmacy students are future stewards of antibiotic use, particularly in LMICs like Indonesia. However, no validated tool exists to assess their knowledge on AMR. This study developed and validated the Antibiotic Knowledge Assessment Questionnaire (AKAQ) using Rasch analysis to support targeted educational efforts.

1.3 Rationale for Study III: Clinical Efficacy of Favipiravir in COVID-19

Favipiravir emerged as a potential COVID-19 treatment but lacks consistent clinical evidence and regulatory approval. This study conducts a meta-analysis on its efficacy in viral clearance among patients with mild to moderate COVID-19.

1.4 Rationale for Study IV: Telepharmacy Readiness in Indonesia

Telepharmacy can address healthcare access gaps in Indonesia's remote regions but remains underutilized and poorly integrated. This study assesses pharmacists' knowledge, perception, and readiness to support its implementation..

1. OBJECTIVES

2.1. Comparison of outpatient antibiotic use in elderly population of Hungary and Sweden

2.1.1. To compare the scale, pattern and seasonality of antibiotic use in elderly patients in ambulatory care settings between Hungary and Sweden

2.2. Antibiotic knowledge assessment questionnaire in undergraduate pharmacy students

2.2.1. To develop a valid and reliable instrument to measure Indonesian undergraduate pharmacy students' general knowledge of antibiotics, antibiotic resistance, and antibiotic stewardship.

2.3. Favipiravir in treatment of mild to moderate COVID-19: A meta-analysis

2.3.1. To systematically review and meta-analyze the available evidence on the clinical efficacy and safety of favipiravir in treating mild to moderate COVID-19

2.4. Pharmacist's knowledge, perception, and readiness toward Telepharmacy

2.4.1. To investigate the level of knowledge, perception, and readiness among pharmacists for telepharmacy

2.4.2. To identify associated sociodemographic factors related to knowledge, perception, and readiness among Indonesian pharmacists toward telepharmacy.

2. METHODS

3.1. *Comparison of outpatient antibiotic use in elderly population of Hungary and Sweden*

3.1.1. Study Design and Setting

A retrospective and descriptive cross-national comparative study was conducted to collect data on antibacterial prescriptions dispensed at community pharmacies in Hungary and Sweden in 2017. Antibacterials were classified according to the anatomical therapeutic chemical (ATC) classification system defined by the World Health Organization (WHO) version 2022. The use of systemic antibacterials (ATC: J01) was measured as prescriptions per 1000 inhabitants per year or per month. The study population included the elderly population (aged >65 years) of Hungary and Sweden in 2017, with 1,828,226 elderly individuals in Hungary and 1,976,857 in Sweden (data derived from Eurostat). These populations were further stratified into subgroups according to age (65–69 years, 70–74 years, 75–79 years, 80–85 years, and >85 years) and sex. Seasonal variation in antibiotic consumption was also assessed.

3.1.2. Description of Databases

Hungarian data were sourced from the National Health Insurance Fund, which captures all reimbursed ambulatory prescriptions, covering ~95% of antibacterial use. Swedish data were obtained from the Swedish eHealth Agency, providing complete records of all outpatient antibiotic prescriptions regardless of reimbursement. Both databases offer nearly 100% national population coverage. Prescriptions included those issued by GPs, specialists, dentists, and private practices. Statistical analyses were performed using Excel, and data visualization was conducted with the R software (version 4.1.2)..

3.2. *Antibiotic knowledge assessment questionnaire in undergraduate pharmacy students*

A cross-sectional study was conducted in Indonesia between February and May 2022 to develop and validate the Antibiotic Knowledge Assessment Questionnaire (AKAQ). The questionnaire was distributed online via Google Forms to undergraduate pharmacy students across multiple universities and semesters. A total of 500 students were recruited using random sampling, with assistance from university lecturers who helped disseminate the instrument. Participant responses were compiled and exported into SPSS version 26.0 for descriptive analysis and into Winsteps version 5.2.1.0 for Rasch modeling.

The questionnaire was developed through a four-step process: framework construction, item generation, expert screening, and pre-testing. The framework was informed by existing AMR surveys and antimicrobial stewardship guidelines. The final version consisted of 29 closed-ended items covering three domains: general antibiotic knowledge, antibiotic resistance, and stewardship. Items were rated using “agree,” “disagree,” or “don’t know” options. Content validity was confirmed by four expert pharmacists, and pre-testing among 30 students was used to refine clarity and format. CVI thresholds (I-CVI ≥0.78, S-CVI ≥0.8/0.9) were met for item inclusion.

Psychometric validation was performed using Rasch analysis. This included assessment of item and person fit (infit/outfit MNSQ 0.5–1.5, ZSTD −2 to +2), unidimensionality (variance >30%, eigenvalue <3), and reliability (Cronbach's alpha >0.6, person/item reliability >0.67). Separation indices (item >3.0, person ≥1.5) indicated strong discriminatory power. The Wright map assessed alignment between item difficulty and participant ability, while Differential Item Functioning (DIF) was used to detect potential bias between early and late semester groups (1st–5th vs. 6th–12th semester). These analyses demonstrated the validity and reliability of the AKAQ for assessing antibiotic knowledge among pharmacy students.

3.3. *Favipiravir in treatment of mild to moderate COVID-19: A meta-analysis*

3.3.1. Study Design and Protocol

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement was used to guide the report of this meta-analysis (77). The study protocol was prospectively registered in PROSPERO under the reference number CRD4202232443 (www.crd.york.ac.uk).

3.3.2. Inclusion criteria

Eligibility was defined using the PICOS framework: P: patients with mild-to-moderate COVID-19; I: favipiravir; C: placebo, standard of care, or other antivirals; O: time to viral clearance; S: randomized controlled trials. According to WHO definitions, mild cases included symptomatic patients (e.g., fever, cough, dyspnea, fatigue) without pneumonia or hypoxia and no imaging abnormalities, while moderate cases showed clinical and radiographic signs of pneumonia but SpO_2 remained ≥90% on room air. Viral clearance was defined as two consecutive negative RT-PCR results ≥24 hours apart. Secondary outcomes included clinical recovery (e.g., sustained symptom resolution, normalized vitals, or improved WHO status for ≥72 hours), imaging improvement, hospitalization, ICU admission, ED visits, and mortality. Safety outcomes assessed laboratory changes (e.g., hyperuricemia, elevated ALT/AST, leukopenia, low hemoglobin) and adverse effects, e.g. gastrointestinal symptoms, respiratory complaints, rash, headache, dizziness, and myalgia.

3.3.3. Search strategy

A systematic literature search was conducted across PubMed, Embase, Web of Science, and the Cochrane Library to identify randomized controlled trials (RCTs) on favipiravir for COVID-19, published up to January 6, 2023. The search used two main keywords: "COVID-19" and "favipiravir". For PubMed, a structured query was built using MeSH terms, synonyms, and Boolean operators (AND, OR), which was then adapted for use in the other databases. Reference tracking was performed on eligible articles, including relevant systematic reviews and meta-analyses. Only full-text articles were included, with no language restrictions. Duplicate records were removed using Rayyan (http://rayyan.qcri.org).

3.3.4. Record screening, Data extraction, and Study risk of bias assessment

Titles and abstracts were screened independently by two reviewers. Full texts of potentially eligible studies were evaluated, with discrepancies resolved through discussion or adjudication by a third reviewer. Inter-rater agreement was quantified using Cohen's kappa (κ) and percentage concordance.Data were extracted independently by two reviewers

using a pre-piloted data extraction form. Information extracted included study characteristics (authors, year, country, study design), patient characteristics (number, age, sex), disease severity (mild or moderate), setting of care (inpatient or outpatient), drug information of intervention and comparator (dose, route of administration, duration), onset of symptoms to randomization, and parameters of efficacy and safety parameters. The Cochrane Risk-of-Bias tool was applied independently by two reviewers to assess methodological quality. Disagreements were resolved through discussion, with a third reviewer consulted if necessary.

3.3.7. Statistical analysis

A random-effects meta-analysis was conducted using RevMan 5.4.1. Hazard ratios (HRs) and risk ratios (RRs) were used for time-to-event and binary outcomes, respectively; risk differences (RDs) were used when appropriate. Heterogeneity was assessed using I^2 statistics and Chi-squared tests ($I^2 > 50\%$, $p < 0.1$ indicating significant heterogeneity). Subgroup and sensitivity analyses were performed to explore sources of variability. Publication bias was examined using funnel plots and Egger's test.

3.4. *Pharmacist's knowledge, perception, and readiness toward Telepharmacy*

3.4.1. Study design and participants

A cross-sectional study was conducted from August 1–7, 2022, using an online survey distributed across all 34 provinces of Indonesia. All licensed pharmacists currently practicing and willing to participate voluntarily were eligible.

3.4.2. Instruments

A validated 24-item questionnaire developed by Kusuma et al. (Appendix 4.1 and 4.2) was used to assess pharmacists' knowledge, perception, and readiness (KPR) for telepharmacy, alongside sociodemographic data (age, gender, education, work experience, and location). The instrument comprised 8 knowledge items (Cronbach's alpha = 0.961), 8 perception items ($\alpha = 0.959$), and 8 readiness items ($\alpha = 0.931$). Knowledge was scored dichotomously (1 = correct, 0 = incorrect), while perception and readiness used a 5-point Likert scale. Scores were standardized to a 0–100% scale, categorized as low (<50%), moderate (50–70%), and high (>70%) levels. Likert responses were also classified into 5 categories ranging from "strongly disagree" to "strongly agree". The survey-based study was approved by the Health Research Ethics Committee of Universitas Harapan Bangsa, Indonesia (approval number: B.LPPM-UHB/955/05/2022).

3.4.4. Procedures

Data collection involved several steps. First, we sent a request letter to the Central Indonesian Pharmacists Association (*Ikatan Apoteker Indonesia Pusat* [IAI]). Second, after obtaining permission from the IAI Central, the IAI assisted in the data collection process. Third, the letter of invitation to participate in our survey was distributed to the branch heads of IAI groups in the 34 provinces in Indonesia through the WhatsApp application; the provinces were divided into three regions according to the time zone.

3.4.5. Data analysis

Data were analyzed using SPSS version 26. Descriptive statistics summarized participant characteristics. Bivariate analysis identified associations between sociodemographic variables and KPR scores. Multivariate ordinal logistic regression was used to assess independent predictors of KPR, with variables from bivariate analysis ($p < 0.25$) included. Results were presented as odds ratios with 95% confidence intervals; p-values < 0.05 indicated statistical significance.

4. RESULTS

4.1. *Comparison of outpatient antibiotic use in elderly population of Hungary and Sweden*

1.1.2. The Scale of Antibiotic Use

The entire Hungarian population (approximately 9.8 million people) was dispensed 6,792,714 prescriptions of antibiotics in 2017, 17.5% of which were dispensed to the elderly. Concurrently, the entire Swedish population (approximately 10 million people) was dispensed 3,204,838 prescriptions of antibiotics, 33.6% of which were dispensed to the elderly. The antibiotic exposure was 649.8 prescriptions/1000 inhabitants/year in Hungarian and 545.0 prescriptions/1000 inhabitants/year in the Swedish elderly population. Figure 2 presents the level of antibiotic exposure across the elderly age subgroups. The antibacterial exposure of the Hungarian elderly population was similar across all age subgroups, while a stepwise increase was observed in antibacterial exposure by age subgroups (an increase from 398 [65–69 years old] to 852 (>85 years old) prescriptions/1000 inhabitants/year) in the Swedish elderly population.

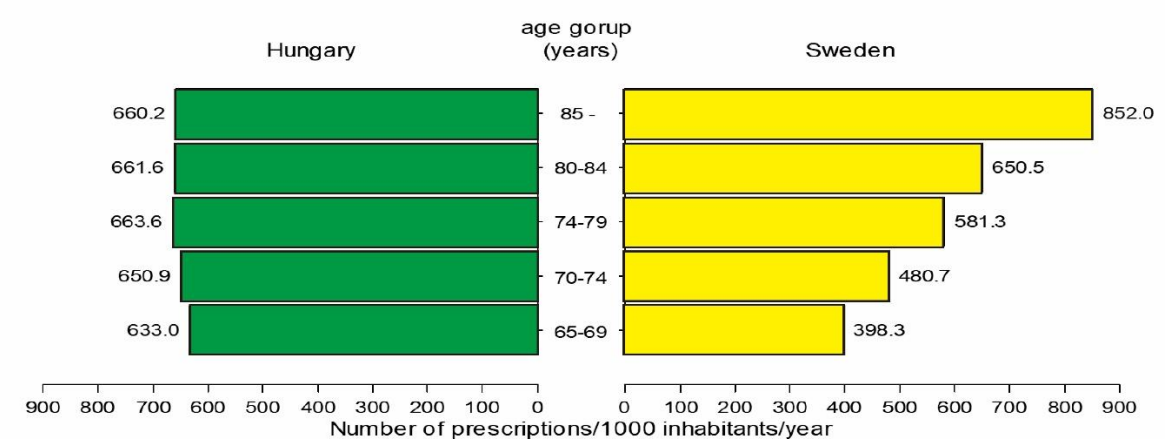

Figure 2. Antibacterial use in different elderly age subgroups in Hungary and Sweden (2017)

4.1.2. The Pattern of Antibiotic Use

Table 2 shows the absolute and relative use of different antibacterial subgroups. Concerning the beta-lactam antibacterials, the penicillin group was responsible for one-fifth of total ambulatory care antibiotic use in the elderly in Hungary, and cephalosporins also had considerable use and share. In contrast, the penicillin group was responsible for almost half of antibiotic use in the elderly in Sweden, and marginal cephalosporin use was observed. The absolute and relative use of macrolides and fluoroquinolones were considerably higher in the Hungarian elderly population than in the Swedish counterparts, with an opposite pattern for tetracyclines and other antibacterials because their use was higher in the Swedish elderly (Table 2).

Table 3 shows the top ten list of antibacterials. Amoxicillin and clavulanic acid (co-amoxiclav) and two fluoroquinolones (levofloxacin and ciprofloxacin) covered almost half (46.6%) of the antibiotic use of the Hungarian elderly population in ambulatory care, whereas 40% of all antibiotics used by the elderly population in ambulatory care constituted of the narrow-spectrum penicillin V, flucloxacillin, or pivmecillinam in Sweden. Nitrofurantoin use was almost absent in Hungary but constituted approximately 10.5% of the elderly antibiotic use in Sweden.

Table 2. Absolute and relative use of antibiotic subgroups in the elderly population in Hungary and Sweden

	Hungary	Sweden
J01A Tetracyclines	15.46 (2.38%)	52.84 (9.7%)
J01C Beta-lactam antibacterials, penicillins	141 (21.7%)	260.53 (47.81%)
J01CA Penicillins with extended spectrum	*15.12 (2.33%)*	*105.03 (19.27%)*
J01CE-CF Narrow-spectrum penicillins	*1.90 (0.29%)*	*145.55 (26.71%)*
J01CR Penicillin combinations	*123.99 (19.08%)*	*9.96 (1.83%)*
J01D Other beta-lactam antibacterials	75.45 (11.61%)	9.14 (1.68%)
J01DB First-generation cephalosporins	*0.60 (0.09%)*	*8.79 (1.61%)*
J01DC Second-generation cephalosporins	*58.36 (8.98%)*	*0.01 (>0.01%)*
J01DD Third-generation cephalosporins	*16.49 (2.54%)*	*0.26 (0.05%)*
J01E Sulfonamides and trimethoprim	36.18 (5.57%)	28.56 (5.24%)
J01EA Trimethoprim and derivatives	-	*13.93 (2.56%)*
J01EE Sulfonamides & trimethoprim Combinations	*36.18 (5.57%)*	*14.63 (2.68%)*
J01F Macrolides, lincosamides, and streptogramins	120.06 (18.48%)	32.41 (5.95%)
J01FA Macrolides	*82.86 (12.75%)*	*8.41 (1.54%)*
J01FF Lincosamides	*37.20 (5.72%)*	*24.00 (4.4%)*
J01M Quinolones	224.38 (34.53%)	54.41 (9.98%)
J01X Other antibacterials	36.17 (5.57%)	106.96 (19.63%)
J01XE Nitrofuran derivatives	*0.02 (>0.01%)*	*57.17 (10.49%)*
J01XX Other antibacterials	*36.12 (5.56%)*	*49.09 (9.01%)*
Other	1.11 (0.17%)	0.11 (0.02%)
Total (J01)	**649.81 (100%)**	**544.96 (100%)**

Unit = Prescriptions/1000 inhabitants/year

Table 3. The top ten list of antibacterials used in the elderly population in Hungary and Sweden (2017)

Hungary	Prescriptions/1000 inhabitants/year	Percentage	**Sweden**	Prescriptions/1000 inhabitants/year	Percentage
amoxicillin/ clavulanic acid	123	18.95	phenoxymethyl penicillin	81.5	14.95
levofloxacin	95.8	14.75	pivmecillinam	72.3	13.27
ciprofloxacin	83.9	12.92	flucloxacillin	64.0	11.75
azitromycin	57.1	8.78	nitrofurantoin	57.2	10.49
cefuroxim	48.2	7.42	ciprofloxacin	52.8	9.68
clindamycin	37.2	5.72	methenamine	48.5	8.90
SMX/TMP*	36.2	5.57	doxycycline	47.9	8.80
fosfomycin	36.1	5.56	amoxicillin	32.7	6.00
norfloxacin	24.5	3.78	clindamycin	24.0	4.40
clarithromycin	23.3	3.59	SMX/TMP*	14.6	2.68

*SMX/TMP, sulfamethoxazole and trimethoprim

4.1.3. Sex-Specific Antibiotic Use

Overall, elderly females used more antibiotics than elderly males in Hungary and Sweden. Elderly females have been exposed to antibiotics at 668 prescriptions/1000 elderly females/year in Hungary, while elderly males at 620 prescriptions/1000 elderly males/year. Swedish elderly females were exposed to antibiotics at 618 prescriptions/1000 females/year, while elderly males at 460 prescriptions/1000 males/year in ambulatory care (Figure 3).

However, the antibiotic exposure of the two sexes of the elderly population showed opposite trends in the age subgroup analysis in Hungary (Figure 3). Antibiotic use decreased from 685 prescriptions/1000 females/year (60–65 years old) to 631 prescriptions/1000 females/year (>85 years old) in Hungary. Conversely, the scale of antibiotic use in the Hungarian elderly male increased by age [from 563 prescriptions/1000 males/year (65–69 years old) to 739 prescriptions/1000 males/year (>85 years old)]. Both elderly females and males in Sweden were exposed to increasing amounts of antibiotics by increasing age (Figure 2 and Figure 3) and in all elderly subgroups Swedish females were exposed to more antibiotics than Swedish males).

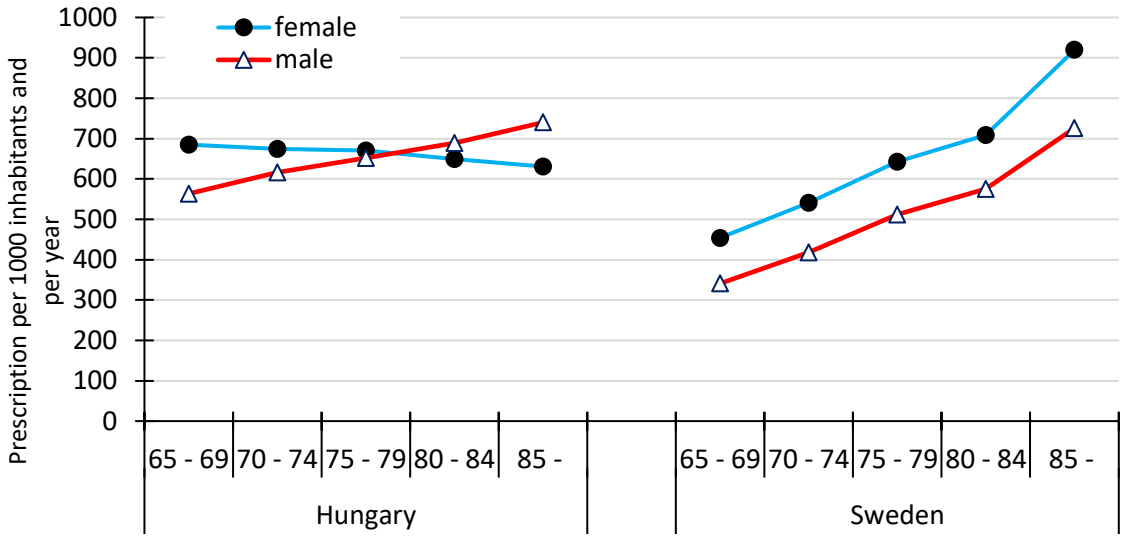

Figure 3. Sex-specific use of antibiotics in ambulatory care presented by age subgroups in the elderly population in Hungary and Sweden (2017)

4.1.4. Seasonal Variation

Figure 4 shows the seasonal variation in antibiotic use in the elderly in Hungary and Sweden. The seasonal fluctuation was high in Hungary, reaching a peak of 80.7 prescriptions/1000 inhabitants/month in January. The lowest value in Hungary was 39.2 prescriptions/1000 inhabitants/month in July. Antibacterial use in the elderly population in Sweden was more equally distributed over the entire year, with a peak consumption of 49 prescriptions/1000 inhabitants/month in March and a nadir of 42 prescriptions/1000 inhabitants/month in April.

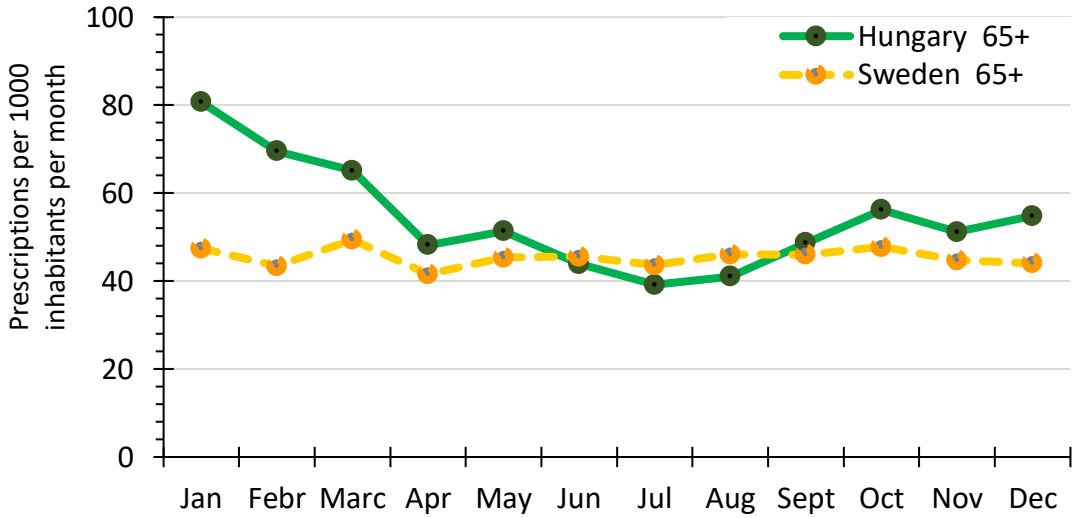

Figure 4. Seasonal variation of antibiotic use among the elderly population in Hungary and Sweden in 2017

1.2. *Antibiotic knowledge assessment questionnaire in undergraduate pharmacy students*

4.2.1. Data Collection and Screening

A total of 500 AKAQ participants from 90 Indonesian universities completed the questionnaire (Table 4). Among the participants, 85% were females; 59% were 20–23 years old; 30.4% were in the fourth semester. Most participants (69.0%) were from universities in the western region of Indonesia where most of the universities are located.

Table 4. Demographics of Participants (n=500)

Baseline Characteristics	Frequency	%
Sex		
Female	425	85%
Male	75	15%
Age		
<20 years old	117	35.4%
20-23 years old	294	58.8%
>23 years old	29	5.8%
Semester		
1^{st} – 5^{th} Semester	282	56.4%
6^{th} – 12^{th} Semester	218	43.6%
University Participants		
West Region (69 Univ.)	345	69.0%
Central Region (20 Univ.)	126	25.2%
East Region (1 Univ.)	29	5.8%

4.2.2. AKAQ Validity and Reliability

The Person and Item Fit Parameters are summarized in Table 5. Overall, the average of infit (weight) and outfit (unweight) mean square (MNSQ) values (0.93 and 1.00), and z-standard (ZSTD) (0.03 and 0.06), were within acceptable thresholds. However, 11% of participants (n = 56) were misfits (see Appendix 2.3) (infit/outfit MNSQ outside 0.5–1.6 with positive PTMA) and were excluded. After deletion, fit statistics improved with MNSQ and ZSTD person values were 0.95 and 1.02, and 0.11 and 0.08, respectively. For item fit statistics, all mean values were within recommended boundaries (infit MNSQ = 1.00, outfit MNSQ = 0.93; ZSTD = −0.30 and 0.09, respectively) except one misfitting item (K7; MNSQ: 0.17; ZSTD: −2.18) (see Appendix 2.4), which was subsequently removed (see Appendix 2.5). Post-deletion, item fit indices improved across both MNSQ and ZSTD (see Table 5). Although 10 misfit items exceeded the ZSTD threshold (see Appendix 2.4), this is acceptable for large sample sizes (>200). Final 28 items fit orders are shown in Figure 5.

The Y-axis represents item difficulty based on Joint Maximum Likelihood Estimation, and the X-axis shows Item Fit MNSQ. Each bubble corresponds to an item, with its size proportional to the standard error of item difficulty calibration. Items that fall close to the vertical line indicate good fit, with outfit MNSQ values in the acceptable range (x = 0.50–1.50). Items with MNSQ values exceeding 1.50 indicate overfit.

Table 5. The Summary of Rasch Parameters for AKAQ

	Persons	Person (After deletion of 56 person misfits)	Item (question)	Item (After deletion item K7)
N	500	444	29	28
Mean Measure	0.78	0.75	0.00	0.16
SD	0.80	0.69	1.61	1.41
SE	0.04	0.04	0.31	0.27
Mean:				
Infit MNSQ	1.00	1.02	1.00	1.01
	(0.43-1.69)	*(0.61-1.69)*	*(0.82-1.16)*	*(0.89-1.16)*
Infit ZSTD	0.03	0.11	0.09	0.11
	(-2,85-2.5)	*(-1.90-2.44)*	*(-2.72-4.46)*	*(-2.72-4.46)*
Outfit MNSQ	0.93	0.95	0.93	0.96
	(0.14- 2.73)	*(0.50-1.58)*	*(0.17-1.24)*	*(0.73-1.24)*
Outfit ZSTD	0.06	0.08	-0.30	-0.23
	(-1.33-2.80)	*(-1.13-1.27)*	*(-2.55-2.85)*	*(-2.55-2.85)*
Reliability (Rasch)	0.73	0.68	0.99	0.99
Reliability (Cronbach's Alpha)	0.71			
Separation Coefficient	1.65	1.44	10.83	11.40
Unidimensionality				
Raw variance by measure	34.9%			
Unexplained variance in 1st contrast	2.84%			

*SD= Standard Deviation, SE= Standard error, MNSQ= mean-square, ZSTD= z-standard, K7= Knowledge Question no.7

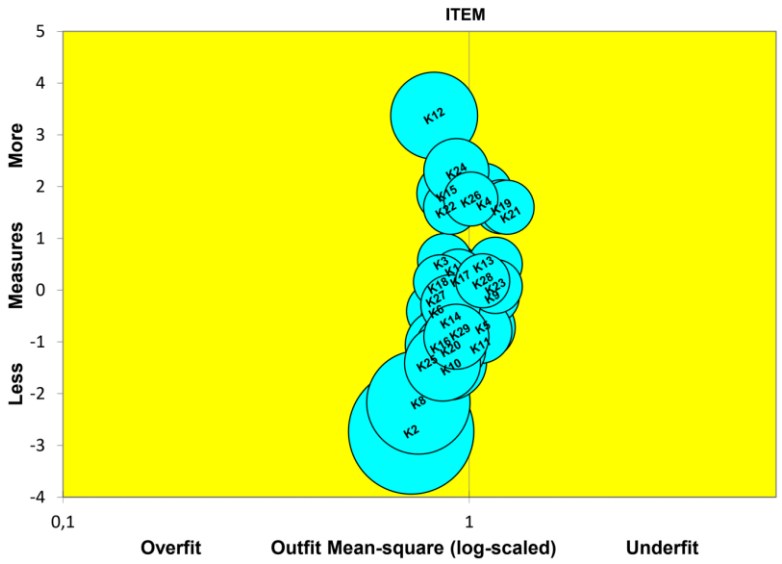

Figure 5. Bubble Chart of Item Fit Order

4.2.3. Construct validity (unidimensionality)

The structural validity of the AKAQ was further examined using unidimensionality. The results achieved an acceptable threshold at >30% (33.4%), which indicates that the instrument achieves unidimensionality criteria. Moreover, the unexplained variance for the first contrasting values was <3% (2.71%). The unexplained variance confirms no random noise in the instrument used in this study.

4.2.4. Reliability

The Rasch parameter generated acceptable criteria for person and item reliabilities, i.e., 0.7 and 0.9, respectively. Additionally, Cronbach's Alpha was above the acceptable threshold, i.e., 0.6 (Table 5). Overall, the AKAQ exhibited acceptable criteria for the Rasch reliability parameter. Moreover, the person and item separations were acceptable, i.e., 1.44 and 20.08, respectively. These values supported the idea of the AKAQ reliability.

4.2.5. Item-person interaction

We presented the item-person Wright map in Figure 6 to check whether the items in the AKAQ are neither too challenging nor too easy for the participants. In this study, the participants' indicators were located higher than the items' indicators, reflecting that pharmacy students had a higher ability than the difficulty level of the items. The difference between the mean person measure and the mean item measure was <1 logit (0.51 logits), indicating that the difficulty level of the items was suitable for the participants' abilities. Hence, we can identify that the item K2 (Bacterial infections can be treated with antibiotics) was the easiest item and item 12 (Beta-lactamases are enzymes produced by bacteria that break open the beta-lactam ring) was the hardest.

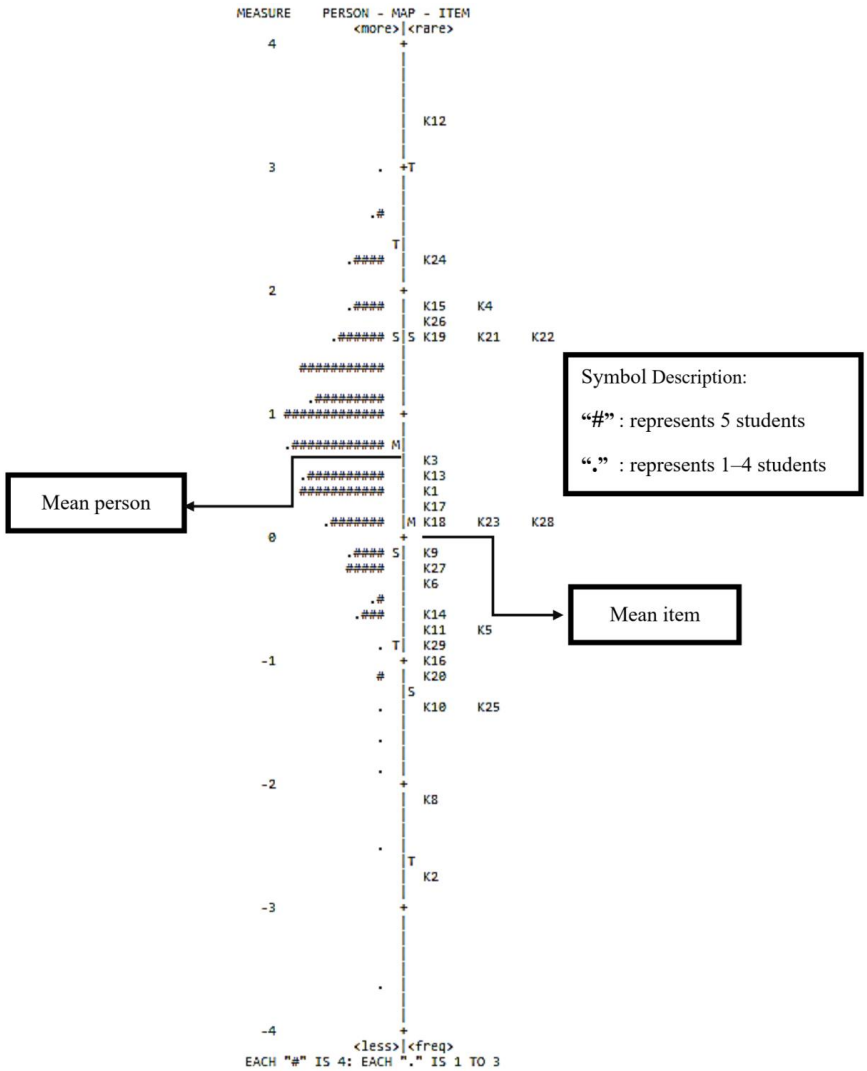

Figure 6. Wright Map (Item-Person Correlation).

The Wright map also shows that students had >50% chance (p = 0.5) of correctly answering an item when their indicator was above the item's indicator. A 50% chance (p = 0.5) occurred when the indicators aligned, indicating comparable difficulty levels between the item and the student's ability. Conversely, students had <50% chance (p < 0.5) of correctly answering the item if their indicator was below the item's indicator.
This map displays the distribution of person ability and item difficulty on the same logit scale. The left side represents individual respondents, with higher positions indicating greater ability. Each "#" symbol denotes five students, and each point "." represents one to four students. The right side displays the 28 questionnaire items, ranked from the easiest (K2, at the bottom) to the most difficult (K12, at the top). The letter "M" indicates the mean person ability (left) and mean item difficulty (right). Items and persons that align closely to the center vertical axis reflect a good match between item difficulty and participant ability.

4.2.6. Differential Item Functioning (DIF) Analysis

DIF analysis by semester (Figure 7) indicated that the items K6 (DIF:0.79; Prob:0.0045) and K19 (DIF: −0.67; Prob: 0.0198) have moderate to large DIF category (see Appendix 2.6). Items K6 and K19 were found to be relatively easier for students in earlier semesters (1st–5th) compared to those in later semesters (6th–12th). This may reflect better recall of basic knowledge recently covered in coursework or greater attentiveness to core topics in the early years of study. However, these items were not dropped because they are relevant to antibiotic-related knowledge, as indicated by content and construct validity results. Dropping these items might reduce the reliability and validity.

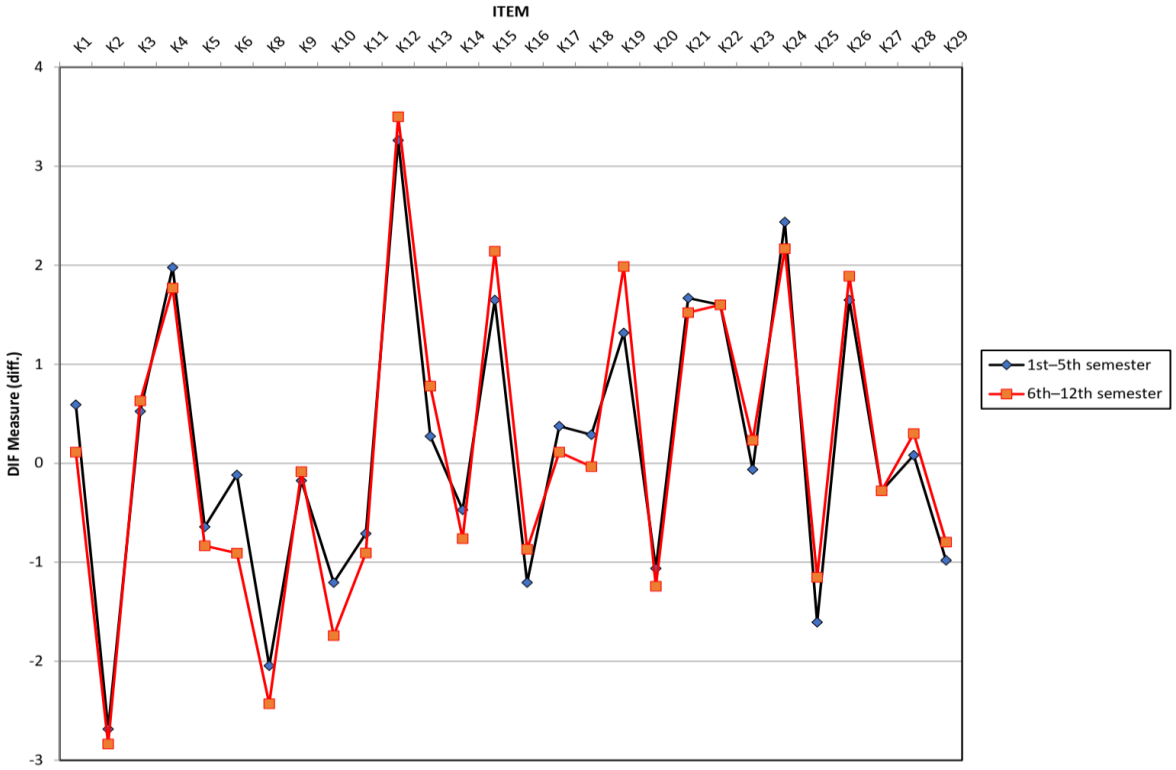

Figure 7. DIF Based on the Semester

1.3. *Favipiravir in treatment of mild to moderate COVID-19: A meta-analysis*

4.3.1. Study selection

The systematic searching queries generated 883, 3334, 984, and 172 hits in PubMed, Embase, Web of Science, and Cochrane Library, respectively. After eliminating duplicate records (n = 1551), 3822 distinct entries were available for title and abstract (TIAB) screening. This first screening stage resulted in 49 eligible records that then entered the second stage of the screening process. The full-text assessment led to the exclusion of 29 articles for several reasons, such as retracted articles (n=2), not eligible study design (n=14), abstract proceeding (n=3), favipiravir combined with another antiviral drug (n=5), wrong comparison (n=1), not eligible disease severity (n=3), and a parenteral drug administration (n=1). Therefore, the final number of articles included was 20 (Figure 8). Reviewer agreement was high: 99.5% at the title/abstract level (κ = 0.71, good) and 96.4% at full-text screening (κ = 0.93, very good).

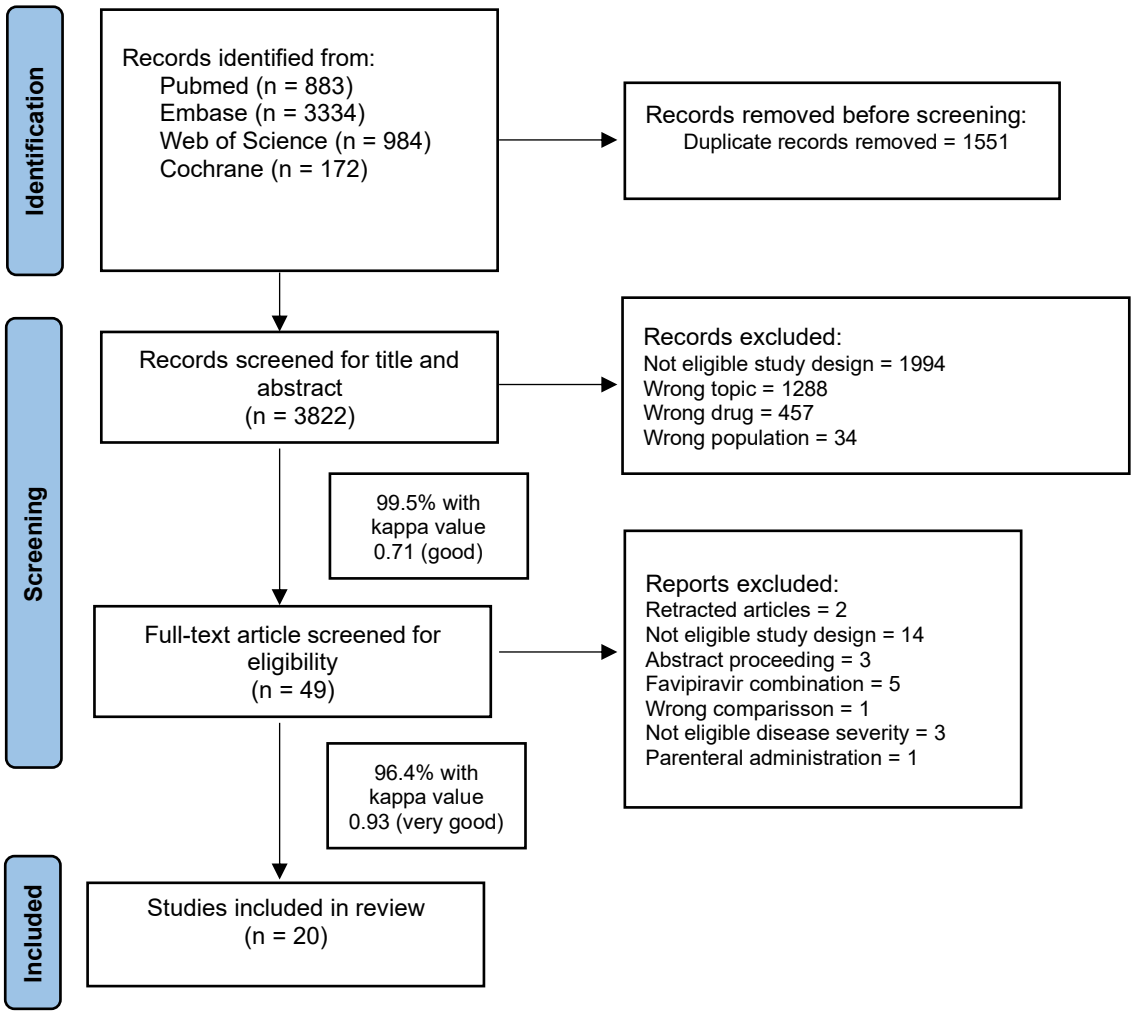

Figure 8. Flow chart of study selection

4.3.2. Study characteristics

Among the 20 eligible articles, 12 were open-label, seven were double-blind, and one was single-blind randomized controlled trials, all involving patients with mild to moderate COVID-19. Study locations were diverse: four in Russia, three in China, and one each in Australia, Bahrain, Bangladesh, India, Iran, Japan, Kuwait, Malaysia, Saudi Arabia, Thailand, the UK, and the USA. One study included multiple countries (Brazil, Mexico, and the USA). Thirteen studies were conducted in inpatient settings, five in outpatient settings, and two in both. All studies administered a loading dose of oral favipiravir on day one (1600–2200 mg, two to three times daily), followed by 1200–1800 mg daily in divided doses for 5 to 14 days. In most studies, randomization occurred within 12 days of symptom onset. The characteristics and outcomes of each study are summarized in Table 6 and Appendix 3.3, respectively. However, three studies did not report the randomization method, and four lacked information on allocation concealment. Additionally, 12 studies were unblinded. A summary and visual representation of the risk of bias are provided in Figure 9 and Appendix 3.4.

1.3.3. Methodological assessments of articles

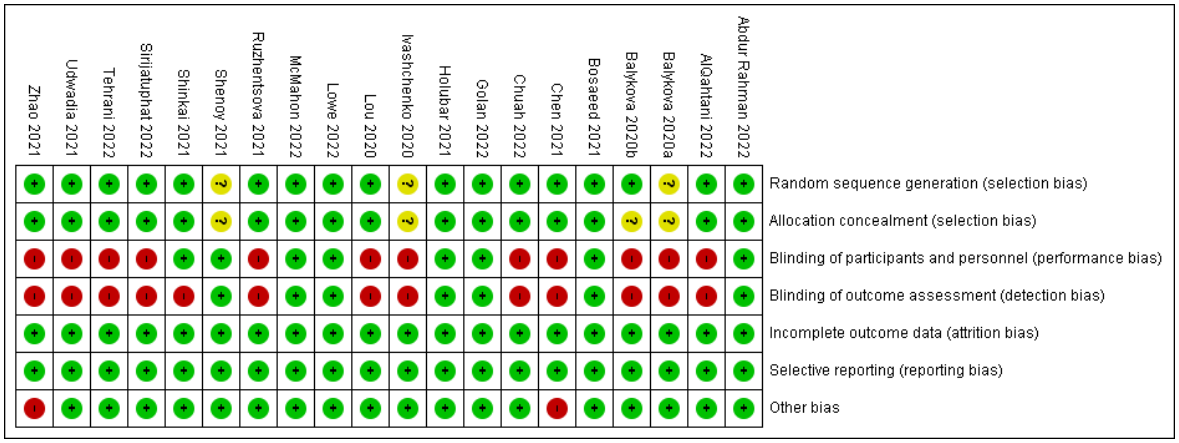

Figure 9. Risk of bias summary of included studies

4.3.4. Primary efficacy outcomes

There were eight studies that reported the Hazard Ratio (HR) for viral clearence (Appendix 3.3). There were no statistically significant differences between the favipiravir and comparator groups in viral clearance (HR = 1.20 [95% CI (Confidence Interval): 0.98-1.47, p=0.09], I^2 (I-squared heterogeneity statistic)=40%) (Figure 10). The subgroup analysis by disease severity showed that favipiravir treatment significantly increased viral clearance by 59% (HR = 1.59 [95% CI: 1.25-2.03, p<0.01], I^2=0%) compared to the comparators in patients with moderate severity of COVID-19 (Figure 11). On the contrary, favipiravir had no significant effects on viral clearance (HR = 0.98 [95% CI: 0.80-1.20, p=0.85], I^2=0%) in COVID-19 patients with mild symptoms (Figure 11).

Table 6. Characteristics of eligible studies

Ref.	Country	Study Design	Number of patients		Age			Sex (Male in %)	Severity	Setting of care	Favipiravir dose	Comparator	Onset to randomization
			Favipiravir (Favi)	Comparator (Comp)	Mean in years(SD)	Median in years (IQR)	Quantity (< 65 years, %)						
Abdur Rahman, 2022	Bangladesh	Double-blinded randomized controlled trial	25	25	Favi: 37.96 (11.45) Comp: 37.54 (10.18)			Favi: 64 Comp: 68	Mild and Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 10th day: 600 mg (bid)	Placebo	Within 7 days
AlQahtani, 2022	Bahrain	Randomized, controlled, open-labeled study	54	51		Favi: 44.5 (33.0, 50.0) Comp: 48.5 (35.5, 57.0)		Favi: 43 Comp: 52	Mild and Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 10th day: 600 mg (bid)	SoC	Within 10 days
Balykova,2020a	Russia	Randomized, open-label, multicenter comparative study	17	22	Favi: 47.1 (2.3) Comp: 47.5 (1.9)			No Infaviormation	Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 14th days: 600 mg (bid)	SoC treatment of COVID-19 in Russian guideline	Hospitalization not exceeding 48 hours before administration of favipiravir
Balykova, 2020b	Russia	Open randomized multicentre comparative study	100	100	Mean Age Ofavi Population: 49.7 (13.1) Range Ofavi Age: 20 To 80			Favi: 50.9 Comp: 49.0	Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 14th day: 600 mg (bid)	SoC treatment of COVID-19 in Russian guideline	Hospitalized not more than 48 hours before the start of the study
Bossaed, 2021	Saudi Arabia	Randomized double-blinded, multicentre placebo-controlled trial	112	119		Favi: 37 (31.5, 45.0) Comp: 37 (32, 44)		Favi: 64.2 Comp: 69.7	Mild	Outpatient	1st day : 1800 mg (9 tab) (bid) 2nd – 5th or 7th days: 800 mg (bid)	SoC + Placebo	Within 5 days of disease onset
Chen, 2021	China	Randomized controlled, open-label multicenter trial	116	120			Favi: 75 Comp: 65.8	Favi: 50.9 Comp: 42.5	Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 7th days: 600 mg (bid)	SoC + Umifenovir: 200 mg (tid)	Within 12 days of initial symptoms

Ref.	Country	Study Design	Number of patients		Age			Sex (Male in %)	Severity	Setting of care	Favipiravir dose	Comparator	Onset to randomization
			Favipiravir (Favi)	Comparator (Comp)	Mean in years(SD)	Median in years (IQR)	Quantity (< 65 years, %)						
Chuah, 2022	Malaysia	Randomized, open-label, parallel, multicenter, phase 3 clinical trial	250	250	Favi: 62.6 (7.51) Comp: 62.4 (8.41)			Favi: 52.4 Comp: 44.4	Mild to moderate	Inpatient	1st day: 1800 mg (bid) 2nd – 5th days: 800 mg (bid)	SoC	Within 7 days
Golan, 2022	USA, Brazil, Mexico	Randomized, multicenter, double-blind, placebo-controlled trial	599	588			Favi (<60, %): 84.5 Comp (<60, %): 86.1	Favi: 47.1 Comp: 44.4	Mild to moderate	Outpatient	1st day: 1800 mg (bid) 2nd – 10th days: 800 mg (bid)	Placebo + SoC	Within 5 days
Holubar, 2021	USA	Randomized, double-blind, placebo-controlled phase 2 trial	59	57	Favi: 42.9 (12.3) Comp: 43.4 (12.8)			Favi: 52.5 Comp: 49.1	Mild	Outpatient	1st day: 1800 mg (bid) 2nd – 10th day: 800 mg (bid)	Placebo + SoC	Positive SARS-CoV2 RT-PCR within 72 hours of enrollment
Ivashchenko, 2020	Russia	Randomized, adaptive, multicenter, open-label, Phase II/III clinical trial	40	20		No Infaviormation		No Infaviormation	Moderate	Inpatient	1st day: 1600 mg (bid) ; 2nd – 14th days: 600 mg (bid); or 1st day: 1800 mg (bid); 2nd – 14th day: 800 mg (bid)	SoC	No information
Lou, 2021	China	Randomized, exploratory single-center, open-label, controlled trial	9	10	Favi: 58.0 (8.1) Comp: 46.6 (14.1)			Favi: 77 Comp: 70	Mild to Moderate	Inpatient	1st day : 1600 mg or 2200 mg (tid) 2nd – 14th days: 600 mg (tid)	SoC	No information
Lowe, 2022	UK	Randomized, Double-blind, 2x2 factorial placebo-controlled trial	59	60	Favi: 40.3 (12.1) Comp: 40.6 (12.2)			Favi: 54.2 Comp: 51.7	Mild	Outpatient	1st day: 1800 mg (bid) 2nd – 7th day: 400 mg (qid)	Placebo + SoC	Within 7 days of symptom onset
McMahon, 2022	Australia	Randomized placebo-controlled phase 2 trial	66	67		Favi: 36 (28-49) Comp: 35 (27.5, 52.5)		Favi: 55.6 Comp: 54	Mild and Moderate	Inpatient and Outpatient	1st day: 1800 mg (bid) 2nd – 14th day: 800 mg (bid)	Placebo + SoC	Within 5 days

Ref.	Country	Study Design	Number of patients		Age			Sex (Male in %)	Severity	Setting of care	Favipiravir dose	Comparator	Onset to randomization
			Favipiravir (Favi)	Comparator (Comp)	Mean in years(SD)	Median in years (IQR)	Quantity (< 65 years, %)						
Ruzhentsova, 2021	Russia	Randomized, open-label, active-controlled trial	112	56	Favi: 41.7 (10.6) Comp: 42.0 (10.4)			Favi: 43.8 Comp: 53.6	Mild and Moderate	Inpatient and Outpatient	1st day : 1800 mg (bid), 2nd – 9th day: 800 mg (bid)	SoC	No more than 6 days
Shenoy, 2021	Kuwait	Randomized, multicentre, double-blind, placebo-controlled, parallel design	175	178			Favi (<50, %): 40 Comp (<50, %): 41.6	Favi: 67.4 Comp: 67.4	Moderate	Inpatient	1st day : 1800 mg (bid), 2nd – 10th day: 800 mg (bid)	Placebo + SoC	Within 10 days
Shinkai, 2021	Japan	Randomized, single-blind, placebo-controlled, parallel-group design	107	49	Favi: 43.8 (12.5) Comp: 48.7 (14.1)		Favi: 94.4 Comp: 85.7	Favi: 71.0 Comp: 57.1	Moderate	Inpatient	1st day: 1800 mg (bid) 2nd – 13th day: 800 mg (bid)	Placebo + SoC	Within 10 days
Sirijatuphat, 2022	Thailand	Multicentre, open-labelled, randomized control study	62	31		Favi: 32 (27-39) Comp: 28 (25, 35)		Favi: 33.9 Comp: 38.7	Mild	Inpatient	1st day: 1800 mg (bid) 2nd – 14th day: 800 mg (bid)	SoC	Within 10 days
Tehrani, 2022	Iran	Randomized, open-label, controlled clinical trial,	38	40	Favi: 53.08 (11.80) Comp: 51.95 (13.34)			Favi: 52.6 Comp: 57.5	Moderate	Outpatient	1st day: 1600 mg (bid) 2nd – 4th day: 600 mg (bid)	SoC	Within 3-9 days
Udwadia, 2021	India	Randomized, open-label, parallel-arm, multicenter trial	72	75	Favi: 43.6 (12.2) Comp: 43.0 (11.2)			Favi: 70.8 Comp: 76.0	Mild and Moderate	Inpatient	1st day : 1800 mg (bid), 2nd – 14th day: 800 mg (bid)	SoC	No more than 7 days
Zhao, 2021	China	Multicenter open-label, randomized controlled trial	36	19	Favi: 55.8 (13.6) Comp: 55.5 (12.6)			Favi: 44.4 Comp: 47.4	Mild and Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 7th days: 600 mg (bid)	SoC	No information

Abbreviations: Favi = Favipiravir group; Comp = Comparator group; SoC = Standard of Care; RCT = Randomized Controlled Trial; bid = twice daily; IQR = Interquartile Range; SD = Standard Deviation.

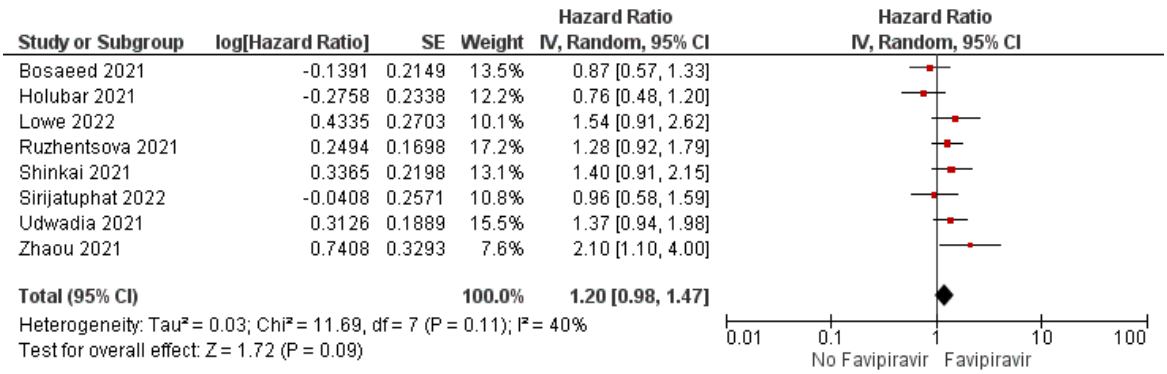

Figure 10. Favipiravir had no significant effect on viral clearance compared to comparator

The results of subgroup analysis by healthcare settings indicated that the favipiravir group had significantly higher viral clearance (HR = 1.42 [95% CI: 1.11-1.82, p<0.01], I^2=20%) in the inpatient care setting than in the comparator groups (Appendix 3.5). However, in the outpatient care setting, the comparable results for the viral clearance (HR = 1.01 [95% CI: 0.77-1.33, p=0.93], I^2=36%) showed no significant effect of favipiravir (Appendix 3.5).

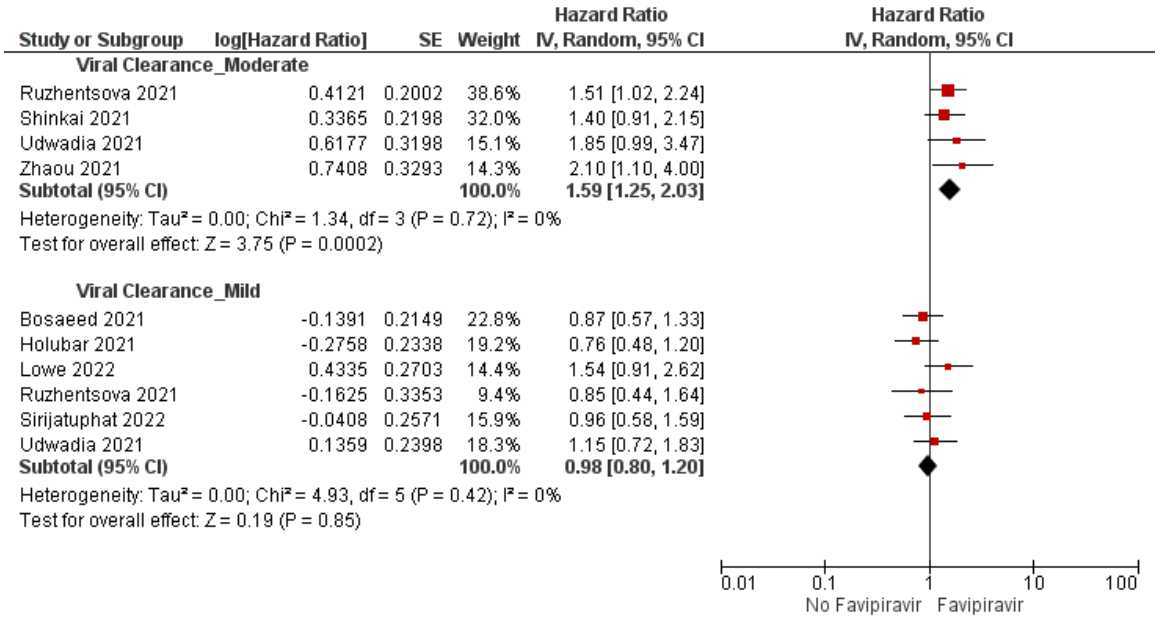

Figure 11. Favipiravir was more effective in terms of viral clearance in moderate, but not in mild severity.

These results are also supported by the analysis of the proportion of patients who achieved viral clearance rather than the time to viral clearance. There were 13 studies that contained information on relative risk (RR) for viral clearance (Appendix 3.3). Achieved viral clearance was significantly higher in the groups treated with favipiravir with moderate severity (RR = 1.16 [95% CI: 1.02-1.32, p<0.01], I^2=0%) and in those who were treated in the hospital (RR = 1.17 [95% CI: 1.06-1.28, p<0.01], I^2=18.9%) than in the case of the comparators (Appendix 3.6.a and Appendix 3.7.a). This efficacy was not observed in the group treated with favipiravir with mild COVID-19 (RR = 1.01 [95% CI: 0.95-1.07, p=0.84], I^2=41.9%) and in those who were treated in ambulatory care (RR = 1.04 [95% CI: 0.92-1.17, p=0.51], I^2=26.7%) compared to the comparator groups (Appendix 3.6.b and Appendix 3.7.b).

4.3.5. Secondary efficacy outcomes

There were 16 studies that reported clinical improvement as an indicator to demonstrate the effectiveness of favipiravir. However, those studies used various parameters to define clinical improvements (Table 7). Seven studies indicated that favipiravir significantly increased the likelihood of clinical recovery compared to the comparators. Among these studies, five studies demonstrated that favipiravir increased clinical cure in patients with COVID-19 with moderate symptoms significantly compared to the comparator groups. There was only one study indicating that favipiravir significantly improved the clinical condition of COVID-19 patients with mild symptoms compared to the control group. Another study did not have a subgroup analysis by severity.

Ten studies did not support that favipiravir was associated with a better clinical improvement than the comparators. Five studies provided evidence for patients with mild symptoms and three studies for patients with moderate symptoms. There studies did not provide a subgroup analysis by severity.

All studies reported at least one of the other secondary outcomes that can be pooled in the meta-analysis (Appendix 3.3). The use of favipiravir was associated with a greater improvement in chest imaging (RR = 1.23 [95% CI: 1.03-1.45, p=0.02], I^2=20%) than in the comparator group (Appendix 3.8a). There were no significant differences between the two groups for other outcomes such as mortality (RD = -0.00 [95% CI: -0.01-0.00, p=0.88], I^2=0%), emergency department visits (RR = 1.15 [95% CI: - 0.50-2.66, p=0.74], I^2=28%), hospitalization's (RR = 1.05 [95% CI: - 0.54-2.05, p=0.89], I^2=35%), ICU (RR = 1.24 [95% CI: - 0.67-2.32, p=0.49], I^2=0%), and hospital discharge (RR = 1.09 [95% CI: - 0.96-1.24, p=0.20], I^2=76%) (Appendix 3.8b-g). The result for hospital discharge had substantial heterogeneity. Therefore, we performed a sensitivity analysis excluding one study, which decreased heterogeneity; however, the difference was still not significant (RR = 1.04 [95% CI 0.97-1.12, p=0.23], I^2=14%) (Appendix 3.8g).

Table 7. Effects of favipiravir on clinical improvement

Reference	Parameters	Results		
		Overall severity COVID-19	**Mild severity COVID-19**	**Moderate severity COVID-19**
Favorable for favipiravir (Favi)				
Balykova, 2020b	The proportion of patients who achieved clinical scale ≤ 2 in the WHO 8-Category Ordinal Scale (transfer to outpatient or complete recovery)			RR: 1.34, 95% CI: 1.15-1.56 ; FAVI: 90% SoC: 67%
Chen, 2021	Clinical recovery rate: based on the recovery of temperature, respiratory rate, oxygen saturation, and cough relief.			RR: 1.28, 95% CI: 1.04-1.57 FAVI: 71.43% SoC + Umifenovir: 55.86% Rate ratio: 0.1557 (95% CI: 0.03-0.28, p value=0.02)
Ruzhentsova, 2021	Time to a reduction of patient clinical status on at least 1 score according to the WHO 8-Category Ordinal Scale compared to baseline.	HR: 1.63, 95% CI: 1.14-2.34 Median time FAVI: 6 days (IQR: 4-9.25 days) SoC: 10 days (IQR: 5-21 days) RR: 1.26, 95% CI: 1.02-1.54 FAVI: 83.03% SoC: 66.10%		HR: 1.66, 95% CI: 1.09-2.52
Shinkai, 2021	Time to improvement in four clinical parameters: temperature, SpO_2, chest imaging, and viral clearance (two consecutive negative results separated by at least 24 h).			HR: 1.59, 95% CI: 1.02-2.48 Median time FAVI: 11.9 days (95% CI: 10.0–13.1) Placebo: 14.7 days (95% CI: 10.5–17.9) RR: 1.32, 95% CI: 1.02-1.73 FAVI: 75.70% SoC: 57%
Sirijatuphat, 2022	Time to sustained clinical improvement by a National Early Warning Score (NEWS) of ≤1 for at least 7 days		HR: 2.77, 95% CI: 1.57- 4.88 Median time FAVI: 2 days Control: 14 days Range of 1–28 days for both groups RR: 2.45, 95% CI: 1.45-4.15 FAVI: 79% SoC: 32.3%	
Tehrani, 2022	Respiratory rate at the end of study (day 7 after treatment)	F: 21.08±2.92 SoC: 19.3±1.60 P< 0.01		
Udwadia, 2021	Time to clinical cure: according to clinician assessment and clinical	HR: 1.75, 95% CI: 1.10- 2.79 Median time		HR: 2.09, 95% CI: 1.06-4.15 Median time

Reference	Parameters	Results		
		Overall severity COVID-19	**Mild severity COVID-19**	**Moderate severity COVID-19**
	parameters such as normalization of fever, respiratory rate, oxygen saturation as well as cough relief persisted for ≥72 h.	FAVI: 3 days (95% CI: 3-4 days) Control: 5 days (95% CI: 4-6 days) RR: 1.02, 95% CI: 0.94-1.12 FAVI: 96.22% SoC: 93.90%		FAVI: 3.5 days (95% CI: 3-4 days) Control: 6 days (95% CI: 4-12 days) RR: 1.09, 95% CI: 0.92-1.30 FAVI: 95.83% SoC: 87.50%
Unfavorable for favipiravir (FAVI)				
AlQahtani, 2022	The proportion of patients who recovered based on a clinical scale < 2 at the end of the study (hospital discharge)	RR: 1.03, 95% CI: 0.86-1.23 FAVI: 83.33% SoC: 80.77%		
Bosaeed, 2021	Time to clinical recovery: normalization of temperature and respiratory symptoms, as well as the suppression of the cough, persisted for at least 72 hours.	-	HR: 0.89, 95% CI: 0.64-1.25 Median time FAVI: 7 days (IQR: 4-11 days) Placebo+SoC: 7 days (IQR: 5-10 days)	-
Chuah, 2022	Rate of clinical progression from nonhypoxia to hypoxia	RR:1.24, 95% CI: 0.84–1.85 FAVI: 18.40% SoC: 14.80%	RR: 1.38, 95% CI: 0.71-2.67 FAVI: 14.84% SoC: 10.74%	RR: 1.01, 95% CI: 0.60-1.70 FAVI: 18.85% SoC: 18.60%
Golan, 2022	Time to sustained clinical recovery: based on oxygen saturation, oral temperature, and all COVID-19-associated symptoms for four consecutive days	Median time FAVI: 7 days (95% CI: 7-8 days) Control: 7 days (95% CI: 6-8 days) Proportion: RR:1.01, 95% CI: 0.96–1.05 F: 87.8% SoC: 87.3%		
Holubar, 2021	Time to sustained symptom resolution: first of two consecutive days without symptoms.		HR: 0.87, 95% CI: 0.52-1.45 Median time FAVI: NA (95%CI: 26, NA) Placebo+SoC: 24 days (95%CI: 21, NA)	
Lou, 2021	Time to an improvement of two points on a seven category the National Early Warning Score 2 (NEWS2) or live discharge from the hospital, whichever came first.			Median time FAVI: 14 days (IQR: 6-38 days) Control: 15 days (IQR: 6-24 days) RR: 1.11, 95% CI: 0.47-2.60 FAVI: 55.55% SoC: 50.00%
McMahon, 2022	Time to virological cure (two successive swabs negative for SARS-CoV-2 by PCR)	Time to virological cure: Log-rank p = 0.6 Fever: Log-rank p = 0.3 Cough: Log-rank p = 0.6 Sore throat: Log-rank p = 0.7		

Reference	Parameters	Results		
		Overall severity COVID-19	**Mild severity COVID-19**	**Moderate severity COVID-19**
	Time to symptom resolution (fever, cough, sore throat, fatigue)	Fatigue: Log-rank p = 0.4		
Ruzhentsova, 2021	Time to a reduction of patient clinical status on at least 1 score according to the WHO 8-Category Ordinal Scale compared to baseline.		HR: 1.60, 95% CI: 0.78-3.26	
Shenoy, 2021	Time to resolution of hypoxia: attainment of a score of four or lower on the WHO 10-point ordinal scale of clinical status			HR: 1.21, 95% CI: 0.85-1.73 Median time FAVI: 6 days Placebo: 7 days
Udwadia, 2021	Time to clinical cure: according to clinician assessment and clinical parameters such as normalization of fever, respiratory rate, oxygen saturation as well as cough relief persisted for ≥72 h.		HR: 1.47, 95% CI: 0.77-2.81 Median time FAVI: 3 days (IQR: 2-4 days) Control: 4 days (IQR: 3-5 days) RR: 0.97, 95% CI: 0.90-1.03 FAVI: 96.55% SoC: 100%	

Abbreviations: FAVI = Favipiravir; Comp = Comparator; SoC = Standard of Care; RR = Relative Risk; CI = Confidence Interval; HR = Hazard Ratio; IQR = Interquartile Range; NA = Not Available.

4.3.6. Safety outcomes

Seventeen studies reported at least one side effect that can be analysed in the meta-analysis (Appendix 3.3). The risks of developing low haemoglobin, hyperglycemia, elevated ALT and AST, high bilirubin, elevated creatine phosphokinase, high triglycerides, and leukopenia were comparable between the favipiravir and comparator groups (Appendix 3.9). Furthermore, the risks that both groups would experience other symptoms, such as abdominal pain, anorexia, constipation, diarrhea, dizziness, dyspnea, headache, myalgia, nasal congestion, nausea, rhinorrhoea, skin rash and vomiting, were also not significantly different (Appendix 3.10). It is noteworthy that the frequency of these symptoms might be influenced by the disease itself. However, a meta-analysis of ten studies indicated that patients treated with favipiravir were almost six times more likely to develop hyperuricemia than those who did not receive favipiravir (RR = 5.77 [95% CI 3.18-10.47, p<0.01], I^2=56%) (Figure 12). Since heterogeneity was moderate, we performed a sensitivity analysis excluding a study by Holubar et al. (2021). The result indicated that the favipiravir regimen increased the risk of hyperuricemia more than seven times (RR = 7.12 [95% CI: 4.73-10.72, p<0.01], I^2=0%) compared to the comparator treatment. (Appendix 3.11). In general, favipiravir can be considered a safe drug since the incidence of adverse events observed in the favipiravir group was not significantly different from the comparator group, except for the risk of hyperuricemia.

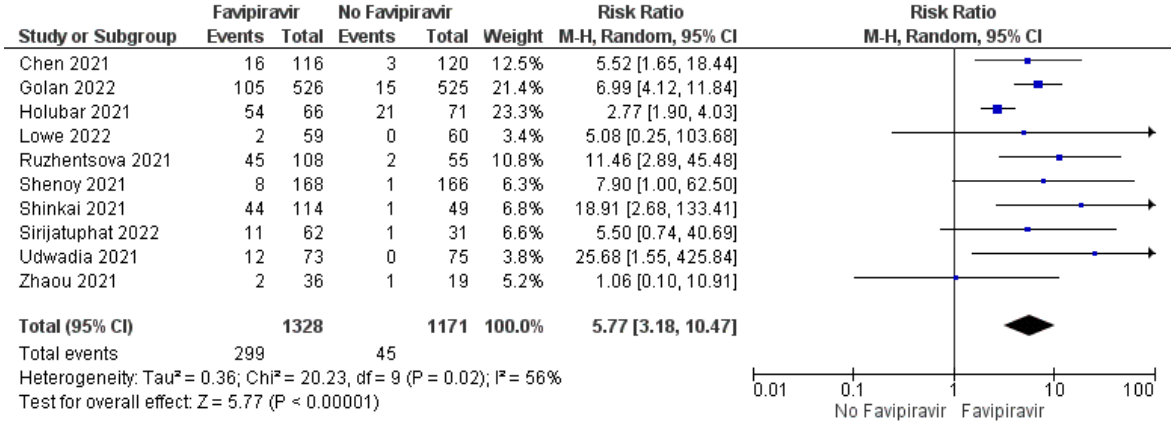

Figure 12. The risk of hyperuricemia is higher in patients treated with favipiravir

4.3.7. Publication bias

The funnel plots for the primary outcome (viral clearance) and the safety outcome (hyperuricemia) were presented in Appendix 3.12a-b. The Egger's regression test results (p>0.05) indicated no publication bias for the outcomes. However, the Cochrane handbook recommended not to use the funnel plot and Egger's regression test if the number of studies included in the meta-analysis of the outcomes is less than ten studies since the test would have a low power to detect the real asymmetry. In our analysis, the number of included studies for viral clearance is below ten.

1.4. *Pharmacist's knowledge, perception, and readiness toward Telepharmacy*

4.4.1. Sociodemographic characteristics of the study participants

The sociodemographic characteristics of the study participants are presented in Table 8. The study involved 6,059 pharmacists from healthcare facilities across Indonesia.

Table 8. Descriptive characteristics of study participants (n = 6,059)

Characteristics	***Number***	***%***
Age	6059	
17-25 years	832	13.73%
26-35 years	3662	60.44%
36-45 years	1241	20.48%
>45 years	324	5.35%
Gender		
Male	1132	18.68%
Female	4927	81.32%
Education level		
Pharmacist	5690	93.91%
Master/ Doctoral	369	6.09%
Field of Work		
Community Pharmacy	3217	53.09%
Hospital	1470	24.26%
Public Health Center	1372	22.64%
Internet Access		
Stable	5109	84.32%
Unstable/Poor	950	15.68%
Residence		
Rural	2068	34.13%
Urban	3991	65.87%
Region		
West Region	4753	78.45%
Central Region	1102	18.19%
East Region	204	3.37%

More than half of the pharmacist were aged between 26–35 years (n = 3,662, 60.44%). There was a predominance of female over male pharmacists (81.32% vs. 18.68%, respectively). The majority of the participants held a pharmacist's degree (n = 5,690, 93.91%), worked in community pharmacy (n = 3,217, 53.09%), had stable Internet access (n = 5,109, 84.32%), resided in urban areas (n = 3,991, 65.87%), and were from the West Region of Indonesia (n = 4,753, 78.45%).

4.4.2. Factors associated with KPR

Of the respondents, 58.28% had a high knowledge level regarding telepharmacy, and only 0.15% of participants had a low level of knowledge (see Table 9). Our data showed that 99.80% of participants responded correctly to K1 "Telepharmacy is the provision of pharmaceutical care at a distance through information and communication technology by

pharmacists," as shown in Figure 13. The lowest rate of correct answers (17.97%) was observed for K5 "Counseling via telepharmacy is more expensive."

Table 9. Knowledge and potential determinants of knowledge toward telepharmacy

	Knowledge (N = 6059)							
Variables	**Low**	**%**	**Moderate**	**%**	**High**	**%**	***p-value***	***OR (CI 95%)***
Total Study Population	**9**	**0.15%**	**2519**	**41.57%**	**3531**	**58.28%**		
Age								
17-25 years	1	0.12%	331	39.78%	500	60.10%		ref.
26-35 years	3	0.08%	1555	42.46%	2104	57.45%	**0.17**	0.90 (0.77-1.05)
36-45 years	3	0.24%	506	40.77%	732	58.98%	0.60	0.95 (0.80-1.14)
>45 years	2	0.62%	127	39.20%	195	60.19%	0.97	0.99 (0.77-1.29)
Gender								
Male	1	0.09%	480	42.40%	651	57.51%	0.58	0.96 (0.85-1.10)
Female	8	0.16%	2039	41.38%	2880	58.45%		ref.
Education level								
Pharmacist	9	0.16%	2350	41.29%	3332	58.55%		ref.
Master/ Doctoral	0	0.00%	169	45.92%	199	54.08%	**0.11**	084 (0.68-1.04)
Field of Work								
Community Pharmacy	8	0.25%	1308	40.66%	1901	59.09%		ref.
Hospital	1	0.07%	634	43.13%	835	56.80%	0.16	0.91 (0.81-1.04)
Public Health Center	0	0.00%	577	42.06%	795	57.94%	0.51	0.96 (0.84-1.09)
Internet Access								
Stable	7	0.14%	2117	41.44%	2984	58.42%		ref.
Unstable/Poor	2	0.21%	402	42.27%	547	57.52%	0.53	0.96 (0.83-1.10)
Residence								
Rural	3	0.15%	848	41.01%	1217	58.85%	0.55	1.03 (0.93-115)
Urban	6	0.15%	1671	41.87%	2314	57.98%		ref.
Region								
West Region	6	0.13%	1982	41.68%	2767	58.19%		ref.
Central Region	2	0.18%	458	41.60%	641	58.22%	0.97	1.00 (0.87-1.14)
East Region	1	0.49%	79	38.92%	123	60.59%	0.59	1.08 (0.81-1.44)

CI = confidence interval. OR = odds ratio. Ref = reference. $p < 0.05$ indicates statistical significance.

Approximately one-third of the participants (34.96%) had high scores regarding perception. Notably, 1.53% and 63.51% of patients exhibited low and moderate levels of perception, respectively (see Table 10). Our results indicate that the highest percentage score on perception was achieved on P5 (86.16%); the participants strongly agreed that pharmacy schools should provide education programs encompassing topics on computational skills, information technology, and telepharmacy to assist in the future utilization of telepharmacy. However, the lowest score (72.43%) was recorded for P4 "Do you think therapy monitoring by telepharmacy would be cost-effective compared to a direct consultation at a pharmacy?" (Figure 14).

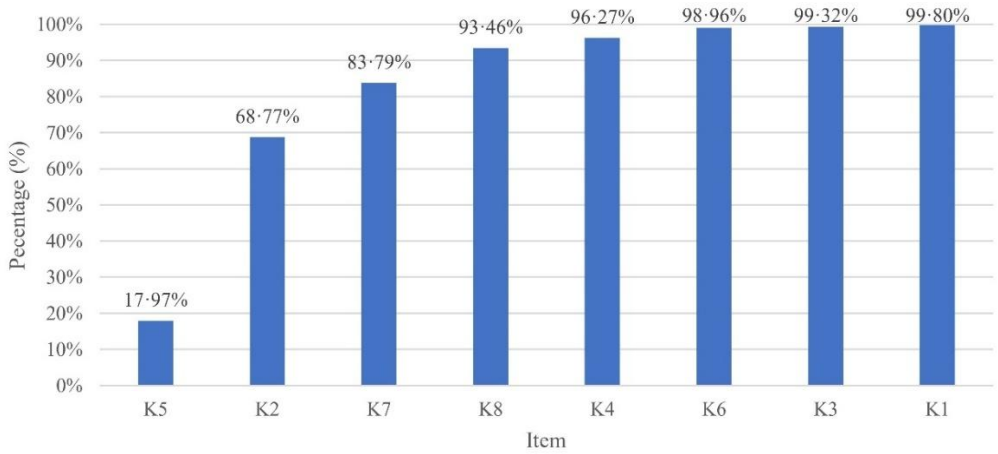

Figure 13. Percentage of correct responses to each knowledge item (K1–K8) regarding telepharmacy (see Appendix 4.2 for item descriptions)

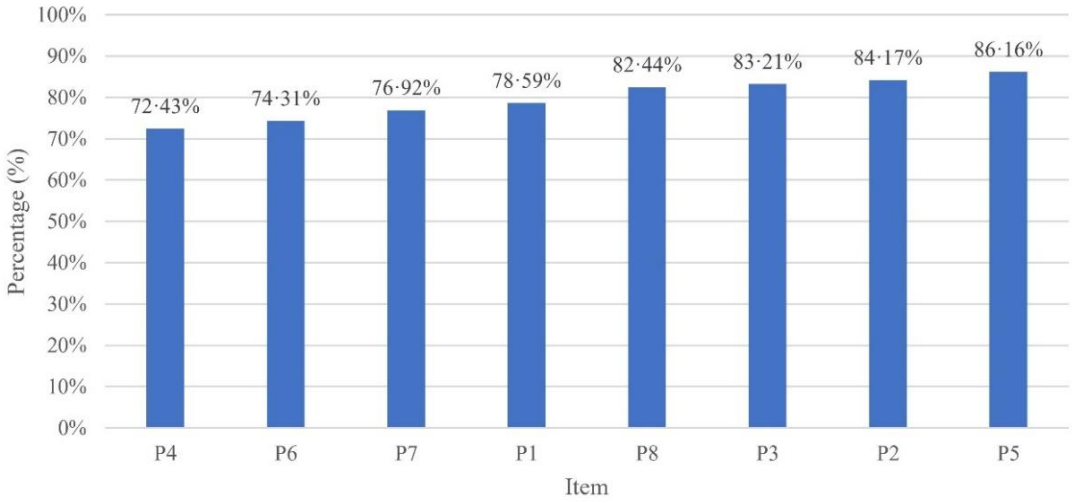

Figure 14. Percentage of "Strongly agree" responses for each perception item (P1–P8) regarding telepharmacy (see Appendix 4.2 for item descriptions)

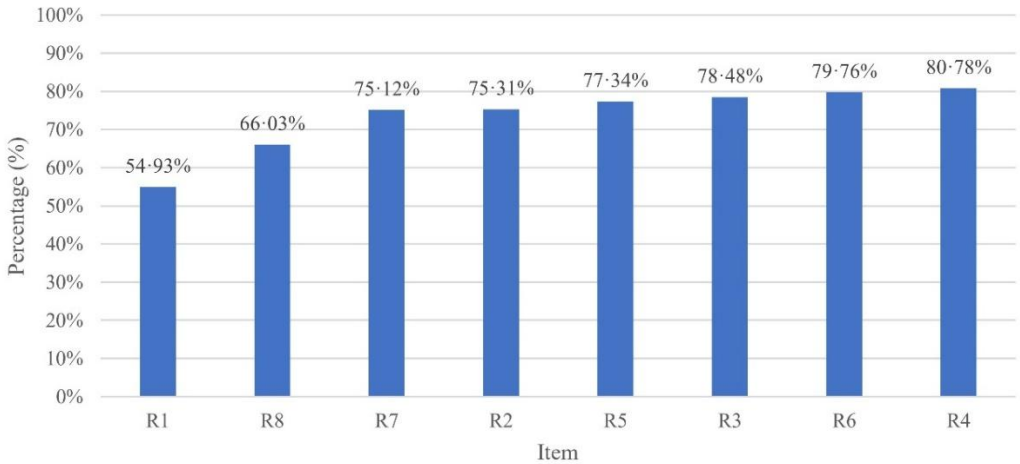

Figure 15. Percentage of "Strongly agree" responses for each readiness item (R1–R8) toward telepharmacy (see Appendix 4.2 for item descriptions)

Table 10. Bivariate analysis of perception and potential determinants of perception toward telepharmacy

	Perception (N = 6059)							
Variables	**Low**	**%**	**Moderate**	**%**	**High**	**%**	***p-value***	***OR (CI 95%)***
Total Study Population	**93**	**1.53%**	**3848**	**63.51%**	**2118**	**34.96%**		
Age								
17-25 years	11	1.32%	540	64.90%	281	33.77%		ref.
26-35 years	58	1.58%	2320	63.35%	1284	35.06%	0.55	1.05 (0.90-1.23)
36-45 years	18	1.45%	803	64.71%	420	33.84%	0.99	1.00 (0.83-1.20)
>45 years	6	1.85%	185	57.10%	133	41.05%	**0.03**	1.33 (1.03-1.73)
Gender								
Male	18	1.59%	675	59.63%	439	38.78%	**<0.01**	1.21 (1.06-1.39)
Female	75	1.52%	3173	64.40%	1679	34.08%		ref.
Education level								
Pharmacist	90	1.58%	3625	63.71%	1975	34.71%		ref.
Master/ Doctoral	3	0.81%	223	60.43%	143	38.75%	**0.09**	1.21 (0.97-1.49)
Field of Work								
Community Pharmacy	59	1.83%	2017	62.70%	1141	35.47%		ref.
Hospital	19	1.29%	921	62.65%	530	36.05%	0.54	1.04 (0.92-1.18)
Public Health Center	15	1.09%	910	66.33%	447	32.58%	**0.13**	0.90 (0.79-1.03)
Internet Access								
Stable	72	1.41%	3201	62.65%	1836	35.94%		ref.
Unstable/Poor	21	2.21%	647	68.11%	282	29.68%	**<0.01**	0.75 (0.64-0.86)
Residence								
Rural	40	1.93%	1359	65.72%	669	32.35%	**<0.01**	0.83 (0.74-0.93)
Urban	53	1.33%	2489	62.37%	1449	36.31%		ref.
Region								
West Region	73	1.54%	3038	63.92%	1642	34.55%		ref.
Central Region	18	1.63%	670	60.80%	414	37.57%	**0.07**	1.13 (0.99-1.29)
East Region	2	0.98%	140	68.63%	62	30.39%	0.28	0.85 (0.63-1.14)

CI = confidence interval. OR = odds ratio. Ref = reference. $p < 0.05$ indicates statistical significance.

As shown in Table 11, 24.34%, 70.21%, and 5.45% of participants demonstrated a high, moderate, and low level of readiness for telepharmacy, respectively. According to Figure 15, the highest percentage score on readiness was obtained for item R4. The majority of participants (80.78%) strongly agreed that they are willing to undergo training in ethics and legal issues related to telepharmacy. In contrast, the lowest score (54.93%) was obtained for R1 “I am ready to work on telepharmacy projects even in rural areas without an incentive.”

Table 11. Bivariate analysis of readiness and potential determinants of readiness toward telepharmacy

Variables	Readiness (N = 6059)						*p-value*	*OR (CI 95%)*
	Low	**%**	**Moderate**	**%**	**High**	**%**		
Total Study Population	**330**	**5.45%**	**4254**	**70.21%**	**1475**	**24.34%**		
Age								
17-25 years	34	1.29%	579	22.00%	219	26.32%		ref.
26-35 years	200	5.46%	2559	69.88%	903	24.66%	**0.14**	0.89 (0.76-1.04)
36-45 years	77	6.20%	903	72.76%	261	21.03%	**<0.01**	0.73 (0.61-0.89)
>45 years	19	5.86%	213	65.74%	92	28.40%	0.83	1.03 (0.78-1.36)
Gender								
Male	64	5.65%	751	66.34%	317	28.00%	**0.01**	1.21 (1.05-1.39)
Female	266	5.40%	3503	71.10%	1158	23.50%		ref.
Education level								
Pharmacist	316	5.55%	4008	70.44%	1366	24.01%		ref.
Master/ Doctoral	14	3.79%	246	66.67%	109	29.54%	**0.01**	1.35 (1.08-1.68)
Field of Work								
Community Pharmacy	199	6.19%	2235	69.47%	783	24.34%		ref.
Hospital	61	4.15%	1035	70.41%	374	25.44%	**0.08**	1.13 (0.99-1.29)
Public Health Center	70	5.10%	984	71.72%	318	23.18%	0.86	0.99 (0.86-1.13)
Internet Access								
Stable	264	5.17%	3568	69.84%	1277	25.00%		ref.
Unstable/Poor	66	6.95%	686	72.21%	198	20.84%	**<0.01**	0.78 (0.67-0.91)
Residence								
Rural	131	6.33%	1450	70.12%	487	23.55%	**0.08**	0.90 (0.80-1.01)
Urban	199	4.99%	2804	70.26%	988	24.76%		ref.
Region								
West Region	271	5.70%	3379	71.09%	1103	23.21%		ref.
Central Region	50	4.54%	742	67.33%	310	28.13%	**<0.01**	1.29 (1.12-1.49)
East Region	9	4.41%	133	65.20%	62	30.39%	**0.02**	1.43 (1.06-1.91)

CI = confidence interval. OR = odds ratio. Ref = reference. $p < 0.05$ indicates statistical significance.

Regarding sociodemographic determinants, age, gender, education level, internet access, residence, and region demonstrated p-values < 0.25 in the bivariate analysis. Thus, these factors were included into the multivariate ordinal logistic regression model.

The results of the multivariate ordinal regression revealed that gender, internet access, and region had significant associations with higher perception and readiness scores ($p < 0.05$). Furthermore, age and education level were significantly associated with readiness. Interestingly, the factors were not significantly correlated with knowledge levels regarding telepharmacy (Table 12).

Table 12. Multivariate analysis of independent determinants of knowledge, perception, and readiness toward telepharmacy

Variables	Knowledge		Perception		Readiness	
	p-value	**aOR (95% Cl)**	***p-value***	**aOR (95% Cl)**	***p-value***	**aOR (95% Cl)**
Age						
17-25 years	-	ref.		ref.		ref.
26-35 years	0.20	1.05 (0.89-1.23)	0.57	1.05 (0.89-1.23)	0.12	0.88 (0.75-1.03)
36-45 years	0.74	1.00 (0.83-1.20)	0.97	1.00 (0.83-1.20)	**<0.01**	0.73 (0.60-0.89)
>45 years	0.81	1.26 (0.97-1.65)	0.09	1.26 (0.97-1.65)	0.91	0.98 (0.74-1.30)
Gender						
Male	-	-		ref.		ref.
Female	-	-	**0.01**	0.83 (0.72-0.95)	**0.01**	0.83 (0.72-0.95)
Education level						
Pharmacist		ref.		ref.		ref.
Master/ Doctoral	0.09	1.12 (0.90-1.40)	0.31	1.12 (0.90-1.40)	**0.01**	1.33 (1.06-1.67)
Field of Work						
Community Pharmacy		ref.		ref.		ref.
Hospital			0.89	1.01 (0.89-1.15)	0.15	1.11 (0.96-1.27)
Public Health Center			0.44	0.95 (0.83-1.09)	0.73	1.03 (0.89-1.18)
Internet Access						
Stable	-	-		ref.		ref.
Unstable/Poor	-	-	**<0.01**	0.79 (0.67-0.92)	**<0.01**	0.75 (0.64-0.89)
Residence						
Rural	-	-		ref.		ref.
Urban	-	-	0.05	1.13 (1.00-1.28)	0.72	1.02 (0.90-1.16)
Region						
West Region	-	-		ref.		ref.
Central Region	-	-	**0.04**	1.16 (1.01-1.33)	**<0.01**	1.29 (1.12-1.49)
East Region	-	-	0.65	0.93 (0.69-1.26)	**<0.01**	1.57 (1.16-2.12)

aOR = adjusted odds ratio. CI = confidence interval. Ref = reference. $p < 0.05$ indicates statistical significance.

5. CONCLUSION

This thesis provides significant insights into cross-national drug utilization patterns, pharmacy education among Indonesian undergraduate pharmacy students, clinical evidence through meta-analysis, and digital healthcare innovation across multiple countries and contexts.

First, the comparative analysis (cross national comparison- CNC) of the scale and pattern of elderly ambulatory antibiotic use revealed differences between Hungary and Sweden. Some of the observed differences could be explained by the different health statuses between the two populations; however, data suggest that interventions are needed to optimize antibiotic use in the elderly in Hungary.

Second, the successful development and validation of the Antibiotic Knowledge Assessment Questionnaire (AKAQ) for undergraduate pharmacy students in Indonesia mark a significant advancement. The AKAQ achieved adequate fit validity and reliability criteria using the Rasch analysis, affirming its psychometric robustness. The instrument shows promise in facilitating targeted educational interventions and advancing antibiotic stewardship initiatives. Further research is required to determine the instrument's applicability across diverse pharmacy students worldwide and various educational levels.

Third, the evaluation of Favipiravir for COVID-19 treatment showed that it did not have a significant effect on the viral clearance rate compared to comparator treatment. Its efficacy could be demonstrated in a subgroup analysis of patients with moderate severity COVID-19, however, favipiravir had no significant effects on viral clearance in patients with COVID-19 with mild symptoms and treated in ambulatory care. These results suggest the use of favipiravir as a routine therapy that should be initialized after the diagnosis of COVID-19 is questionable.

Lastly, the study on Indonesian pharmacists' perspectives on telepharmacy revealed high levels of knowledge but moderate perceptions and readiness, influenced by various sociodemographic factors. Gender, internet access, and region of residence were identified as independent determinants of perception, while age, gender, Internet access, education level, and region of residence were significantly associated with readiness. These findings can inform health authorities in Indonesia in developing and implementing effective telepharmacy policies.

In conclusion, this thesis underscores the importance of a) cross-national comparative studies on antibiotic use, b) evidence based synthesis of the results of available randomized controlled trials c) robust psychometric tools, and d) comprehensive assessments of healthcare innovations. The insights gained can contribute to improved healthcare policies and practices,in antimicrobial use (including both antibiotic and antiviral agents), pharmacy education, and telepharmacy. Further research and targeted interventions are essential to continue advancing these areas and enhancing global health outcomes.

PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

1. **Kusuma IY**, Matuz M, Bordás R, Haverinen MJ, Bahar MA, Hajdu E, Visnyovszki Á, Ruzsa R, Doró P, Engi Z, Csupor D, Benkő R. Antibiotic use in elderly patients in ambulatory care: A comparison between Hungary and Sweden. *Frontiers in Pharmacology*. 2022;13:1042418.
2. **Kusuma IY**, Bahar MA, Nuari DA, Prabandari R, Soeharto S, Csupor D. Antibiotic knowledge assessment questionnaire in undergraduate pharmacy students: A Rasch analysis of validity evidence. *Pharmacy Education*. 2024;24(1):54–78.
3. Bahar MA, **Kusuma IY**, Visnyovszki Á, Matuz M, Benkő R, Ferenci T, Szabó BG, Hajdú E, Pető Z, Csupor D. Favipiravir does not improve viral clearance in mild to moderate COVID-19–A systematic review and meta-analysis of randomized controlled trials. *Heliyon*. 2024;10(9).
4. **Kusuma IY**, Muddather HF, Kurnianto AA, Bahar MA, Kurniasih KI, Tololiu KE, Schelz Z, Zupkó I, Matuz M, Benkő R. Telepharmacy in Indonesia: Navigating knowledge, perception, and readiness among 6000 pharmacists and related sociodemographic determinants. *Telemedicine and e-Health.* 2024.

PRESENTATIONS RELATED TO THE SUBJECT OF THE THESIS

1. **Kusuma IY**, Matuz M, Bordás R, Haverinen MJ, Bahar MA, Hajdu E, Visnyovszki Á, Ruzsa R, Doró P, Engi Z, Csupor D, Benkő R. 2022. Antibiotic Exposure of A Vulnerable Population: Consumption Of The Elderly. 4th International Conference on Pharmaceutical and Medical Sciences. Martin, Slovakia. September 16-18, 2022.
2. **Kusuma IY**, Matuz M, Bordás R, Haverinen MJ, Bahar MA, Hajdu E, Visnyovszki Á, Ruzsa R, Doró P, Engi Z, Csupor D, Benkő R. 2022. Outpatient fluoroquinolone use in elderly population of two European countries. European Drug Utilization Research Group (EuroDURG) Conference 2022. Prague, Czech Republic. October 19-21, 2022. Abs: *International Journal of Clinical Pharmacy*, 44 (6): 1553-1553.
3. Bahar MA, **Kusuma IY**, Visnyovszki Á, Matuz M, Benkő R, Ferenci T, Szabó BG, Hajdú E, Pető Z, Csupor D. 2022. The efficacy and safety of favipiravir in the treatment of nonsevere COVID-19: a systematic review and meta-analysis of randomized controlled trials. European Drug Utilization Research Group (EuroDURG) Conference 2022. Prague, Czech Republic. October 19-21, 2022. Abs: *International Journal of Clinical Pharmacy*, 44 (6): 1491-1491.
4. **Kusuma IY**, Bahar MA, Nuari DA, Prabandari R, Soeharto S, Csupor D. 2023. Antibiotic related knowledge of pharmacy students: questionnaire development and validation with Rasch analysis. European Drug Utilization Research Group Conference 2023. Bologna, Italy. July 27-30, 2023.