Original Research

Medication appropriateness in elderly patients with chronic respiratory disease: Insights from the medication appropriateness index

Qusai Y. Al-Share ⬤, Afnan A. Abu Shqair ⬤, Rawand A. Khasawneh ⬤, Amal J. Albadawi ⬤, Asmaa Ghneimat ⬤

Abstract

Background: This study was conducted at a respiratory disease outpatient clinic. The Medication Appropriateness Index (MAI) was used to assess potentially inappropriate medication (PIM) prescribing, the prevalence of PIM prescription, explore associated factors, and evaluate the reliability of the MAI in this disease area. **Methods:** A cross-sectional study at King Abdullah University Hospital (KAUH), a tertiary teaching hospital in Jordan. It included data from 70 older adults with chronic respiratory diseases and polypharmacy. The MAI was utilized by two clinical pharmacists to gauge the appropriateness of prescribed medications. Multivariate linear regression was used to analyze the factors influencing PIM prescription, while interrater reliability was assessed using the kappa statistic. **Results:** Among 70 patients (mean age: 74.16±6.45 years), 97.1% had at least one PIM, and 38.7% of the medications were deemed inappropriate. Polypharmacy correlated independently with increased MAI scores (OR:3.739; p<0.001). Good interrater agreement (κ=0.6) was observed. **Conclusion:** A high PIM prescription prevalence existed among older adults with chronic respiratory diseases (CRDs) and polypharmacy in respiratory outpatient settings. Polypharmacy significantly correlated with PIM prescription. The MAI demonstrated validity and reliability in identifying medication inappropriateness. These findings emphasize the need for tailored interventions to optimize medication management in this vulnerable population.

Keywords: respiratory diseases; polypharmacy; potentially inappropriate prescribing; pharmacist; Medication Appropriateness Index

INTRODUCTION

Over the past few decades, there has been a significant increase in the average age of the general population,[1-3] with geriatrics (aged 65 and older) encompassing higher percentages of inhabitants worldwide.[4-5] The aging population is facing an increased incidence of CRDs,[6] which requires additional medical care[7,8] and higher healthcare expenses.

Pharmacotherapy for older adults poses significant challenges

Qusai Y. AL-SHARE*. R.Ph., Ph.D, Assistant Professor, Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, P.O. Box 3030, Irbid 22110, Jordan. qyshare@just.edu.jo
Afnan A. Abu-SHQAIR. PharmD, MSc. Lecturer, Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, P.O. Box 3030, Irbid 22110, Jordan. aaabushqair21@ph.just.edu.jo
Rawand A. KHASAWNEH. PharmD. Associate Professor, Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, P.O. Box 3030, Irbid 22110, Jordan. rakhasawneh@just.edu.jo
Amal J. ALBADAWI. BSc, MSc. Lecturer, Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, P.O. Box 3030, Irbid 22110, Jordan. ajalbadwi@just.edu.jo
Asma GHNEIMAT. PharmD, Head, Department of Clinical Pharmacy, King Abdullah University Hospital P.O. Box 20, Irbid 22110, Jordan. aghnaimat@kauh.edu.jo

due to age-related physiological changes affecting medication pharmacokinetics and pharmacodynamics.[9] These changes contribute to heightened sensitivity and adverse drug reactions (ADRs).[9] Considering these changes is crucial for preventing major drug-related problems (DRPs) in older adults.[10] The most significant clinical pharmacokinetic alteration in older adults is the reduction in glomerular filtration rate (GFR).[11,12] Reduced renal clearance has clinically important consequences on drugs that are mainly removed by the kidneys.[13]

Drug-related problems, including PIM prescription, medication underuse, polypharmacy, ADRs, and nonadherence, are linked to increased morbidity, mortality, prolonged hospital stays, higher treatment costs, and decreased quality of life (QoL)[14-16]. PIMs are medications that have high risk-benefit ratios with safer alternatives available.[17] Inappropriate prescribing is prevalent in older adults in general, ranging from 11.5% to 62.5%, leading to increased healthcare costs, adverse events, falls, hospitalizations, and mortality.[18-20]

Concerning the evaluation of PIM prescribing, explicit and implicit criteria were used as reliable tools for this purpose. Explicit criteria, such as the American Geriatrics Society Beers criteria and the STOPP, outline medications to avoid having higher risk-to-benefit ratios.[21] The implicit criteria, such as the MAI, assess PIM prescribing in older adults; considering healthcare professionals' judgement to assess medication appropriateness. The implicit criteria have proven to be valid and reliable with good intrarater and interrater reliability.[22-27]

The present study aimed to assess medication inappropriateness

using the MAI in older adults with CRDs and polypharmacy in a respiratory outpatient clinic. The study sought to determine PIM incidence, explore predictors of PIM prescription, and evaluate the reliability of the MAI in assessing medication appropriateness in this setting.

METHODS

Study Design and Setting:

In this cross-sectional study we collected data from 70 geriatric patients at a respiratory outpatient clinic at King Abdullah University Hospital (KAUH) in Jordan. The study sample was based on similar studies in literature.[28]

Ethical Consideration:

The study was approved by the Institutional Review Board (IRB) of Jordan University of Science and Technology and KAUH in March 2023 (IRB number 26/2023).

Inclusion and Exclusion Criteria:

The inclusion criteria included older adults (≥65 years) with chronic respiratory disease, polypharmacy, who are visiting or had visited the clinic. The exclusion criteria were age <65 years and/or incomplete data.

Data Collection:

Patient data, including demographic information, medical history, diagnoses, and laboratory data were collected. Medication details were collected between January 2021 and April 2023. Required data including medication details were entered on special forms (see Appendix A).

Evaluation of Potential Inappropriate Medication Prescribing

The MAI, validated for reliability, was used to assess appropriateness using nine criteria (excluding cost). Two clinical pharmacists independently reviewed and scored a total of 649 medications from 70 patients. Responses were categorized as (0, 0.5, 1), and inappropriate ratings were multiplied by the criterion weight, yielding a summed MAI score for each medication (0–17) as described by Hanlon et al.[29]

Statistical Analysis

The IBM SPSS version 25.0 was used for analysis. Descriptive statistics are presented as percentages, means±SDs, medians, IQRs, mins, maxs, ranges, and absolute frequencies. A $P<0.05$ value indicated statistical significance.

Predictors of Potential Inappropriate Medication Prescribing

Multivariate linear regression was used to analyze the relationships between demographic/clinical factors and summed MAI score per patient. Odds ratios (95% CI) were determined.

Interrater Reliability

Two raters independently reviewed the data. Interrater reliability was assessed using two-by-two contingency tables, calculating overall percentage agreement (Po%), positive agreement (P-pos), and negative agreement (P-neg). The kappa statistic was used to determine the chance-adjusted agreement and indicated reliability (kappa<0.40: poor; 0.40–0.75: good; >0.75: excellent).[30-32] Items with <10 inappropriate ratings were excluded.

RESULTS

Patient Demographics and Clinical Data

Data from 70 older adults, with a mean age of 74.16±6.45 years (range 65–88), were included in the study. Of the total patients included, 51.4% were women. The mean number of chronic diseases was 4.17±1.44 (median 4.0; range 1–8). The mean number of prescribed medications was 9.27±2.76 (median 9; range 5–15). Notably, 12.9% of patients were prescribed ≥13 medications. The mean GFR was 71.80±27.11 ml/min, and 51.4% exhibited mild renal impairment. The average summed weighted MAI score per patient (MAI score per patient) and per individual medication (MAI score per medication) were 29.17±17.22 and 3.15±5.02, respectively. Table 1 shows the patients' demographic and clinical characteristics.

Disease and Medication Patterns

In the studied patient population, a total of 292 chronic diseases were found. The predominant chronic diseases were circulatory system diseases (n=100; 34.2%) and respiratory system diseases (n=88; 30.1%). Table 2 presents a breakdown of the 10 most prevalent disease classes.

Table 1. Demographic and clinical characteristics of patients	
Patient Characteristics (n=70)	**Value**

Age in years, n (%)
  Mean±SD
  Range
  65-74
  75-84
  ≥ 85
	
	74.16±6.45
	65-88
	38 (54.3)
	26 (37.1)
	6 (8.6)

Gender, n (%)
  Male
  Female
	
	34 (48.6)
	36 (51.4)

Race, n (%) Caucasian	 70 (100)

Number of Illnesses
  Mean±SD
  Median (IQR)
  Range
Number of patients with illnesses, n (%):
  1-2
  3-4
  ≥ 5 Illnesses, n (%)
	
	4.17±1.44
	4.0 (3.0, 5.0)
	1-8
	
	5 (7.1)
	38 (54.3)
	27 (38.6)

GFR (Abbreviated MDRD, mL/min)
  Mean±SD
  Range
  Normal Renal Function, n (%)
  Mild Renal Impairment, n (%)
  Moderate Renal Impairment, n (%)
  Severe Renal Impairment, n (%)
	
	71.80±27.11
	11-157
	13 (18.6)
	36 (51.4)
	19 (27.1)
	2 (2.9)

Number of medications	
Mean±SD	9.27±2.76
Median (IQR)	9 (7, 11)
Range	5-15
Number of patients with:	
5-8 Medications, n (%)	33 (47.1)
9-12 Medications, n (%)	28 (40.0)
≥ 13 Medications, n (%)	9 (12.9)
Summed MAI Score per patient	
Mean±SD	29.17±17.22
Range	0 - 67
Median (IQR)	27.00 (16.00, 41.25)
MAI Score per individual medication	
Mean±SD	3.15±5.02
Range	0 - 15
Median (IQR)	0 (0, 3)

A comprehensive evaluation of 649 medications revealed that the most commonly prescribed classes were respiratory tract (n=213; 32.8%), cardiovascular (n=180; 27.7%), and gastrointestinal medications (n=59; 9.1%). The leading respiratory medications were fluticasone and salmeterol (n=37; 17.4%), salbutamol (n=36; 16.9%), and tiotropium bromide (n=31; 14.6%). Table 2 shows the details of the top 10 most frequently prescribed medication classes and respiratory medications.

Medication Appropriateness Using the MAI

The vast majority of patients (n=68; 97.1%) had at least one PIM, indicated by one or more inappropriate ratings within the nine MAI criteria for at least one medication. Out of the 649 medications, 251 (38.7%) received one or more inappropriate ratings across the MAI criteria.

Among the 213 assessed respiratory medications, 99 (46.5%) were deemed inappropriately prescribed. Salbutamol (n=25; 25.3%), loratadine (n=20; 20.2%), and fluticasone (n=19; 19.2%) were the most frequently prescribed respiratory medications. Table 3 shows the details of the top 10 most frequently prescribed inappropriate respiratory medications.

Among the 649 medications, 198 (30.5%) were prescribed with incorrect directions, 176 (27.1%) had incorrect duration, and 174 (26.8%) had impractical directions. Conversely, only 8 (1.2%) of the prescribed medications exhibited potential drug-disease interactions. Refer to Table (4) for the number of medications with appropriate, marginally appropriate, or inappropriate scores, as well as patients with inappropriate MAI criteria for at least one medication.

Factors Influencing Potentially Inappropriate Medication Prescribing

Multivariate linear regression analysis was used to explore the potential association between demographic and clinical factors and the summed weighted MAI score per patient. The study revealed that an increase in the number of medications per patient was independently and significantly [95%CI 2.36-4.23] associated with higher MAI scores (OR= 3.739; 95%CI 2.17-5.31; p<0.001). Conversely, the number of chronic diseases a patient had was independently and significantly

Table 3. Most frequently prescribed inappropriate respiratory medications	
Top 10 most frequently prescribed inappropriate respiratory medications	**N (%)**
Salbutamol	25 (25.3)
Loratadine	20 (20.2)
Fluticasone	19 (19.2)
Ipratropium and salbutamol	9 (9.1)
Glycopyrronium	4 (4)
Fluticasone and salmeterol	4 (4)
Tiotropium bromide	4 (4)
Theophylline	4 (4)
Ipratropium Bromide	3 (3)
Others	7 (7.1)
Total	99 (100)

Table 2. Most common diseases and most frequently prescribed medications					
Top 10 Diseases[*]	**n (%)**	**Top 10 Prescribed Medication Classes**[$]	**n (%)**	**Top 10 Prescribed respiratory Medications**	**n (%)**
Circulatory system	100 (34.2)	Respiratory tract	213 (32.8)	Fluticasone and salmeterol	37 (17.4)
Respiratory system	88 (30.1)	Cardiovascular	180 (27.7)	Salbutamol	36 (16.9)
Endocrine, nutritional, and metabolic diseases	34 (11.6)	Gastrointestinal	59 (9.1)	Tiotropium bromide	31 (14.6)
Musculoskeletal system and connective tissue	25 (8.6)	Antidiabetic	52 (8.0)	Fluticasone	23 (10.8)
Genitourinary system	14 (4.8)	Diuretic	43 (6.6)	Loratadine	22 (10.3)
Digestive system	13 (4.5)	Vitamins and Minerals	43 (6.6)	Ipratropium and salbutamol	18 (8.5)
Nervous system	7 (2.4)	Genitourinary	17 (2.6)	Budesonide and formoterol	15 (7.0)
Neoplasms	5 (1.7)	Pain and Inflammation	11 (1.7)	O2 therapy	8 (3.8)
Infectious	2 (0.7)	CNS	9 (1.4)	Glycopyrronium	5 (2.3)
Skin and subcutaneous tissue	2 (0.7)	Other	8 (1.2)	Others	18 (8.5)
Total	292 (100)		649 (100)	Total	213 (100)

Diseases were classified using ICD-10 classification.[45]
[$]Medications were classified using ACT classification.[46]

associated with lower MAI scores (OR= -3.066; 95%CI -6.013 to 0.118; p=0.042). However, age and sex were not significantly associated with MAI scores. Notably, compared to patients in the reference group taking 5-8 medications, patients taking 13 or more medications exhibited increased MAI scores (OR=23.030; 95%CI 11.213:34.848; p<0.001). Table 5 shows the comprehensive presentation of factors associated with inappropriate prescription, as determined by the MAI score.

Interrater Reliability

As shown in Table 6, the agreement between the two raters for the 649 medications, employing dichotomized scores. Of these, 452 (69.6%) medications received concordant appropriate ratings for the indication (column A). Conversely, 136 (21%) medications were deemed inappropriate by both raters for the indication (column D). Disagreement on indication ratings

occurred for 61 (9.4%) medications (columns B and C), with B indicating disagreement favouring Rater 1 and C favouring Rater 2.

The presence of agreement signified that both raters assigned the same score to a medication for a given criterion. Positive agreement (P-pos) represented instances where both raters agreed that a medication was appropriate for each MAI criterion. Negative agreement (P-neg) denoted concordance between raters on a medication's inappropriateness for that criterion.

A kappa value of 0.60 indicated good overall agreement between the two raters (0.40-0.75 signifies good interrater reliability). Notably, the highest kappa values were for treatment duration (0.77), indication (0.76), and effectiveness (0.72), while the lowest was for drug-drug interactions (0.35).

Table 4. Number and percentage of medications with appropriate, marginally appropriate, and inappropriate scores per question and patients with inappropriate MAI criterion for at least one medication

MAI Question	Appropriate		Marginally Appropriate		Inappropriate		Patients with inappropriate MAI criterion in at least one medication
	N	%	N	%	N	%	n (%, 95% CI)
1- Indication	469	72.3	32	4.9	148	22.8	61 (87.1, 77.0-93.9)
2- Effectiveness	443	68.3	51	7.9	155	23.9	61 (87.1, 77.0-93.9)
3- Dosage	435	67.0	52	8.0	162	25.0	62 (88.6, 78.7-94.9)
4- Correct Directions	413	63.6	38	5.9	198	30.5	65 (92.9, 84.1-97.6)
5- Practical Directions	439	67.6	36	5.5	174	26.8	65 (92.9, 84.1-97.6)
6- Potential Drug-drug Interaction	612	94.3	28	4.3	9	1.4	8 (11.4,5.1-21.3)
7- Potential Drug-disease Interaction	638	98.3	3	0.5	8	1.2	7 (10.0, 4.1-19.5)
8-Duplication	617	95.1	3	0.5	29	4.5	20 (28.6, 18.4-40.6)
9- Duration	437	67.3	36	5.5	176	27.1	65 (92.9, 84.1-97.6)
Overall Ratings	4503	77.1	279	4.8	1059	18.1	68 (97.1, 90.1-99.7)

Table 5. Factors associated with inappropriate prescribing as determined by the MAI score

Factor	MAI		
	OR	95% CI	p-value
Age (Years): Overall 65-74 75-84 ≥ 85	0.129 Reference -2.281 0.526	-0.454 - 0.713 Reference -11.137 - 6.574 -14.758 - 15.811	0.659 Reference 0.609 0.945
Gender Male Female	Reference 0.343	Reference -6.968 - 7.653	Reference 0.926
Number of medications: Overall 5-8 9-12 ≥ 13	3.739 Reference 7.268 23.030	2.165 - 5.312 Reference -0.806 - 15.343 11.213 - 34.848	<0.001* Reference 0.077 <0.001*
Number of illnesses: Overall 1-2 3-4 ≥ 5	-3.066 Reference 4.111 0.881	-6.013 - -0.118 Reference -12.397 - 20.618 -16.013 - 17.776	0.042* Reference 0.621 0.917

*: Significant (p <0.05).

Table 6. Interrater agreement for MAI (n=649 medications)								
MAI Question	A	B	C	D	Agreement (%)*	Kappa€	P-pos	P-neg
1-Indication	452	9	52	136	91	0.76	0.98	0.72
2- Effectiveness	444	8	62	135	89	0.72	0.98	0.69
3- Dosage	413	16	76	143	86	0.38	0.96	0.65
4- Correct Directions	392	16	77	164	86	0.68	0.96	0.68
5- Practical Directions	391	14	85	159	85	0.66	0.97	0.65
6- Drug-drug Interaction	606	8	25	10	95	0.35	0.99	0.29
7- Drug-disease Interaction	630	12	6	1	97	0.09$	0.98	0.14$
8-Duplication	570	3	53	23	91	0.42	1.00	0.30
9- Duration	417	9	56	167	90	0.77	0.98	0.75
Overall¥	311	16	99	223	82	0.60	0.95	0.69

P-neg = negative agreement; P-pos = positive agreement
A = appropriate according to both raters; B = appropriate according to rater 1, inappropriate according to rater 2; C = appropriate according to rater 2, inappropriate according to rater 1; D = inappropriate according to both raters
*Agreement (%) = (A + D/A+B+C+D) * 100.[47]
€Kappa statistic is chance-adjusted agreement, a Kappa value less than 0.40 indicates poor inter-rater reliability, 0.40-0.75 indicates good inter-rater reliability and a value greater than 0.75 indicates excellent reproducibility
$Inadequate variability in ratings
¥Medication's overall appropriateness (inappropriate if 1 of the 9 criteria was rated as inappropriate)

Considering all scored medications, the overall interrater agreement percentage was 82%, ranging from 85% to 97% for the individual nine items.

DISCUSSION

Our study aligns with the literature, affirming the challenges posed by polypharmacy in older adults, particularly those with CRDs.[33,34] The prevalence of chronic diseases and medications, escalating with age mirrors established patterns in similar studies.[35] The concerning proportion of patients prescribed 13 or more medications emphasizes the vulnerability of this subgroup to adverse outcomes associated with polypharmacy.[35]

Contributing to the understanding of disease and medication use patterns in older adults, our findings resonate with the prominence of circulatory and respiratory system diseases.[36] This aligns with the literature, stressing the need for tailored interventions for these prevalent conditions.[33] Discrepancies in medication classes and specific drugs, compared with published data, highlight potential regional variations or patient population-specific patterns, underscoring the necessity for context-specific approaches.[37] The predominance of salbutamol as the leading culprit in PIMs in this study aligns with the results of community surveillance, which reported that only 10% of elderly patients handled the inhaler device appropriately.[38]

Concerns about the high prevalence of PIM use in older adults, as raised in previous research were also found resonance in our study.[34] Identifying specific respiratory medications frequently prescribed inappropriately aligns with the call for targeted interventions in this therapeutic area.[33] A comparison with studies using the MAI enriches our understanding of consistent findings across diverse populations and healthcare settings.[34]

The identification of the number of medications as a significant predictor of increased MAI scores in this population aligns with the literature, highlighting the universal challenge of managing polypharmacy in older adults.[35] Conversely, the association between a greater number of chronic diseases and lower MAI scores prompts further exploration into the complex interplay between disease burden and medication appropriateness. The lack of significant associations with age and sex underscores the multifactorial nature of inappropriate prescribing, which is consistent with findings from several other studies.[35,39,40] and different from some others.[41-43] A comparative analysis against studies with similar objectives offers nuanced insights into contextual factors influencing prescribing practices.[33]

The assessment of interrater reliability provides insights into the robustness of the methodology, as it yielded good overall agreement and kappa values consistent with those of studies using similar methodologies for assessing medication appropriateness.[36] Comparison with interrater reliability studies using MAI or similar tools enhances the generalizability of our findings, confirming the tool's reliability in diverse healthcare settings.[36,44]

CONCLUSION

Our study revealed a significant prevalence of PIM prescription in elderly patients with CRDs and polypharmacy in an outpatient setting. The majority of patients exhibited at least one PIM, which was significantly linked with polypharmacy. Furthermore, our findings highlight the efficacy of the MAI in discerning medication appropriateness in older adults in respiratory outpatient settings. The demonstrated good interrater reliability emphasizes the validity and reliability of the MAI, affirming its utility for identifying medication inappropriateness in this patient population. This study lays

the groundwork for future interventions aimed at optimizing medication management in elderly patients with CRDs. Identifying prevalent PIMs and understanding their association with polypharmacy underscore the need for tailored strategies to enhance prescribing practices. Interventions such as targeted educational programs for healthcare providers and the implementation of medication review protocols may help mitigate PIM occurrence. Additionally, the validated MAI has emerged as a valuable tool for ongoing assessments, offering a standardized approach to evaluate and enhance medication

appropriateness in older adults, which can be applied in respiratory outpatient settings. Our findings may pave the way for proactive measures to enhance patient safety and healthcare outcomes in this patient population.

CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest.

References

1. Pokharel S, Raut S, Adhikari B. Tackling antimicrobial resistance in low-income and middle-income countries. BMJ Glob Health. 2019;4(6):e002104. https://doi.org/10.1136/bmjgh-2019-002104
2. McKinn S, Trinh DH, Drabarek D, et al. Drivers of antibiotic use in Vietnam: implications for designing community interventions. BMJ Glob Health. 2021;6(7):e005875. https://doi.org/10.1136/bmjgh-2021-005875
3. Nguyen LV, Pham LTT, Bui AL, et al. Appropriate Antibiotic Use and Associated Factors in Vietnamese Outpatients. Healthcare. 2021;9(6):693. https://doi.org/10.3390/healthcare9060693
4. World Health Organization. Antibiotic resistance [Internet]. 2023 [cited 2023 Oct 6]. Available from: https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistancee
5. Perz JF. Changes in Antibiotic Prescribing for Children After a Community-wide Campaign. JAMA. 2002;287(23):3103. https://doi.org/10.1001/jama.287.23.3103
6. Aricò MO, Valletta E, Caselli D. Appropriate Use of Antibiotic and Principles of Antimicrobial Stewardship in Children. Children. 2023;10(4):740. https://doi.org/10.3390/children10040740
7. Rouusounides A, Papaevangelou V, Hadjipanayis A, et al. Descriptive Study on Parents' Knowledge, Attitudes and Practices on Antibiotic Use and Misuse in Children with Upper Respiratory Tract Infections in Cyprus. Int J Environ Res Public Health. 2011;8(8):3246-62. https://doi.org/10.3390/ijerph8083246
8. Togoobaatar G, Ikeda N, Ali M, et al. Survey of non-prescribed use of antibiotics for children in an urban community in Mongolia. Bull World Health Organ. 2010;88(12):930-6. https://doi.org/10.2471/blt.10.079004
9. Huang SS, Rifas-Shiman SL, Kleinman K, et al. Parental Knowledge About Antibiotic Use: Results of a Cluster-Randomized, Multicommunity Intervention. Pediatrics. 2007;119(4):698-6. https://doi.org/10.1542/peds.2006-2600
10. Pavydė E, Veikutis V, Mačiulienė A, et al. Public Knowledge, Beliefs and Behavior on Antibiotic Use and Self-Medication in Lithuania. Int J Environ Res Public Health. 2015;12(6):7002-16. https://doi.org/10.3390/ijerph120607002
11. Nga DTT, Chuc NTK, Hoa NP, et al. Antibiotic sales in rural and urban pharmacies in northern Vietnam: an observational study. BMC Pharmacol Toxicol. 2014;15(1):6. https://doi.org/10.1186/2050-6511-15-6
12. Larsson M, Kronvall G, Chuc N, et al. Antibiotic medication and bacterial resistance to antibiotics: a survey of children in a Vietnamese community. Tropical Medicine and International Health. 2000;5(10):711-1. https://doi.org/10.1046/j.1365-3156.2000.00630.x
13. Anh NTV, Bang NV, antibiotherapy in children with pneumonia admited into pediatric dipartment of Bach Mai hospital in 2006. Y Hoc TPHCM [Internet]. 2007 [cited 2023 Oct 6];11(4):94–99. Available from: https://yhoctphcm.ump.edu.vn/index.php?Content=ChiTietBai&idBai=9529
14. Esteireiro AS, Morais V, Henriques CJ, et al. Parents Knowledge and Attitudes Towards the use of Antibiotics in Patients within the Paediatric age Range. Pediatr Oncall. 2020;17(2).
15. Paredes JL, Navarro R, Watanabe T, et al. Knowledge, attitudes and practices of parents towards antibiotic use in rural communities in Peru: a cross-sectional multicentre study. BMC Public Health. 2022;22(1):459. https://doi.org/10.1186/s12889-022-12855-0
16. Salama RA, Bader KN, Rahmen AS, et al. Parents Knowledge, attitude and practice of antibiotic use for upper respiratory tract infections in children: a cross-sectional study in Ras Al khaimah, United Arab Emirates. Epidemiol Biostat Public Health. 2022;15(4).
17. General Statistics Office. Statistical Yearbook of Vietnam. Statistical Publishing House; 2021.
18. Alumran A, Hurst C, Hou XY. Antibiotics Overuse in Children with Upper Respiratory Tract Infections in Saudi Arabia: Risk Factors and Potential Interventions. Clinical Medicine and Diagnostics. 2012;1(1):8-16.
19. Alumran A, Hou XY, Hurst C. Assessing the overuse of antibiotics in children in Saudi Arabia: validation of the parental perception on antibiotics scale (PAPA scale). Health Qual Life Outcomes. 2013;11(1):39. https://doi.org/10.1186/1477-7525-11-39
20. Panagakou SG, Theodoridou MN, Papaevangelou V, et al. Development and assessment of a questionnaire for a descriptive cross – sectional study concerning parents' knowledge, attitudes and practises in antibiotic use in Greece. BMC Infect Dis.

2009;9(1):52. https://doi.org/10.1186/1471-2334-9-52

21. Yu M, Zhao G, Stålsby Lundborg C, et al. Knowledge, attitudes, and practices of parents in rural China on the use of antibiotics in children: a cross-sectional study. BMC Infect Dis. 2014;14(1):112. https://doi.org/10.1186/1471-2334-14-112

22. Lugova H, Ivanko O, Chumachenko T, et al. Parental knowledge, attitudes and practices regarding antibiotic use in children with upper respiratory infections in Ukraine. International Journal of Infectious Diseases. 2020;101:59.

23. Teck KC, Ghazi HF, Bin Ahmad MI, et al. Knowledge, Attitude, and Practice of Parents Regarding Antibiotic Usage in Treating Children's Upper Respiratory Tract Infection at Primary Health Clinic in Kuala Lumpur, Malaysia. Health Serv Res Manag Epidemiol. 2016;3:233339281664372. https://doi.org/10.1177/2333392816643720

24. Levy Hara G, Kanj SS, Pagani L, et al. Ten key points for the appropriate use of antibiotics in hospitalised patients: a consensus from the Antimicrobial Stewardship and Resistance Working Groups of the International Society of Chemotherapy. Int J Antimicrob Agents. 2016;48(3):239-6. https://doi.org/10.1016/j.ijantimicag.2016.06.015

25. Al-Dossari K. Parental Knowledge , Attitude and Practice on Antibiotic Use for Upper Respiratory Tract Infections in Children. Majmaah Journal of Health Sciences. 2013 ;1(1):33-45. https://doi.org/10.18295/squmj.2021.21.02.019

26. Al-Ayed MZ. Parents' knowledge, attitudes and practices on antibiotic use by children. Saudi J Med Med Sci. 2019;7(2):93. https://doi.org/10.4103/sjmms.sjmms_171_17

27. Kapoor G, Saigal S, Elongavan A. Action and resistance mechanisms of antibiotics: A guide for clinicians. J Anaesthesiol Clin Pharmacol. 2017;33(3):300. https://doi.org/10.4103/joacp.joacp_349_15

28. Center for disease control and prevention. Be Antibiotics Aware: Smart Use, Best Care [Internet]. 2021 [cited 2023 Oct 6]. Available from: https://www.cdc.gov/patientsafety/features/be-antibiotics-aware.html

29. Grigoryan L, Burgerhof JGM, Haaijer-Ruskamp FM, et al. Is self-medication with antibiotics in Europe driven by prescribed use? Journal of Antimicrobial Chemotherapy. 2006;59(1):152-6. https://doi.org/10.1093/jac/dkl457

30. Tenover FC. Mechanisms of Antimicrobial Resistance in Bacteria. Am J Med. 2006 ;119(6):S3-S10.

31. Kisuule F, Wright S, Barreto J, et al. Improving antibiotic utilization among hospitalists: A pilot academic detailing project with a public health approach. J Hosp Med. 2008;3(1):64-70. https://doi.org/10.1002/jhm.278

32. Ministry of heath. Circular No. 05/2016/TT-BYT regulations on prescription in outpatient treatment [Internet]. 2016 [cited 2023 Oct 6]. Available from: https://thuvienphapluat.vn/van-ban/The-thao-Y-te/Thong-tu-05-2016-TT-BYT-ke-don-thuoc-trong-dieu-tri-ngoai-tru-305126.aspx

33. Awad A, Eltayeb I, Matowe L, et al. Self-medication with antibiotics and antimalarials in the community of Khartoum State, Sudan. J Pharm Pharm Sci. 2005;8(2):326-31.

34. The Prime Minister of Vietnam. Decision No 1121/QĐ-TTG Approval of the national strategy for prevention and control of drug resistance in Vietnam for the period of 2023 – 2030 with a vision towards 2045 [Internet]. 2023 [cited 2023 Oct 6]. Available from: https://thuvienphapluat.vn/van-ban/The-thao-Y-te/Quyet-dinh-1121-QD-TTg-2023-Chien-luoc-quoc-gia-phong-chong-khang-thuoc-tai-Viet-Nam-580479.aspx

35. Alumran A, Hou XY, Sun J, et al. Assessing the construct validity and reliability of the parental perception on antibiotics (PAPA) scales. BMC Public Health. 2014;14(1):73. https://doi.org/10.1186/1471-2458-14-73

36. Okide CC, Grey-Ekejiuba O, Ubaka CM, et al. Parents' Knowledge, Attitudes and Use of Antibiotics in Upper Respiratory Infections in Nigerian Children. African Journal of Biomedical Research. 2020;23(2):213-20. https://doi.org/10.1093/tropej/fmt111

37. Harun GD, Haider R, Haque I, et al. Parental Knowledge, Attitudes, and Practices Regarding Antibiotic Use: A Cross-Sectional Study in Bangladesh. Infect Control Hosp Epidemiol. 2020;41(S1):s342–s342. https://doi.org/10.1038/s41598-024-52313-y

38. Al-Saleh S, Abu Hammour K, Abu Hammour W. Influencing factors of knowledge, attitude, and practice regarding antibiotic use in children with upper respiratory tract infections in Dubai. J Eval Clin Pract. 2020 Feb 12;26(1):197–202. https://doi.org/10.1111/jep.13188

39. Wang J, Sheng Y, Ni J, et al. Shanghai Parents' Perception And Attitude Towards The Use Of Antibiotics On Children: A Cross-Sectional Study. Infect Drug Resist. 2019;12:3259-7. https://doi.org/10.2147/idr.s219287

40. Abu Hammour K, Abu Farha R, Alsous M, et al. Evaluation of risk factors affecting parental knowledge and attitude toward antibiotic use in children with upper respiratory tract infections. Eur J Integr Med. 2018;17:107-1.

41. Shah NM, Rahim MA. Parental knowledge, attitudes, and practices (KAPs) on the use of antibiotics in children for upper respiratory tract infections (URTIs). Int J Pharm Pharm Sci. 2017;9(3):105-10.