

## KAP of Antibiotic Resistance among the Junior Doctors in RIMS

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### Abstract

**Introduction:** WHO Defines The Appropriate Use Of Antimicrobials As “The Cost Effective Use Of Antimicrobials Which Maximizes Clinical Therapeutic Effect While Minimizing Both Drug-Related Toxicity And The Development Of Antimicrobial Resistance.” Antibiotic Resistance (ABR) Is One Of The Major Health Problems In Developing Countries Like India Where Relatively Easy Availability And Higher Consumption Of Antibiotics (AB) Leads To High Level Of ABR. A Better Understanding Of What The Doctors Know And Believe About These Issues Of ABR And Its Usage Can Assist In Planning An Effective Educational Intervention For Them. To The Best Of Our Knowledge There Were No Previous Studies That Analyzed The Knowledge, Attitude And Practice Of Health Care Professionals On AB Use In Manipur. Hence, This Study Was Undertaken Among Junior Doctors In Order To Assess Their Knowledge And Attitude Concerning ABR, As Well As Their Self-Reported Practices In A Tertiary Care Hospital.

**Objectives:** 1. To Assess The Knowledge, Attitude Of Junior Doctors About ABR And Their Self-Reported Practices Related To AB Usage. 2. To Determine The Association Between Knowledge And Attitude Of ABR With Variables Of Interest Like Gender, Designation And Age

**Materials And Methods:** This Was A Cross-Sectional Study Conducted Among All The Junior Doctors (Interns And Junior Residents) In RIMS, Imphal During 23<sup>rd</sup> Feb To 24<sup>th</sup> March '17. A Pretested Self-Administered Semi Structured Validated Questionnaire Was Used To Collect Data. Data Compilation And Analysis Was Done Using Software SPSS 21 Version.

**Results:** Four-Fifth Of The Junior Doctors Revealed That The Contributory Factors For Antibiotic Resistance Were Mainly Due To Inadequate Dosage, Inaccurate Choice And Incomplete Treatment Of Antibiotics. Almost Three-Fourth (71.9%) Junior Doctors Had Poor Knowledge Of Antibiotic Resistance And Its Usage. A Little More Than Half (53.9%) Of The Junior Doctors Had Favorable (Right) Attitude Towards Antibiotic Resistance. Practice : Only A Little More Than Half (53.9%) Always Completed The Full Course Of The Prescribed Treatment And More Than Half (58.70%) Of Our Respondent Never Stop Taking AB In spite Of Feeling Better After 2-3 Doses Of AB. Almost One-Fourth Of The Junior Doctors Did Not Checked The Expiry Dates Before Taking Antibiotics . Resident Doctors Were Found To Have More Knowledge On Antibiotic Resistance As Well As Having Better Attitude Towards Antibiotic Use Than The Internees And Were Found To Be Statistically Significant.

**Conclusion:** 7 Out Of 10 Junior Doctors Had Poor Knowledge Of Antibiotic Resistance And Its Usage. Only Half Of The Junior Doctors Had Favorable Attitude Towards Antibiotic Resistance. 8 Out Of 10 Junior Doctors Revealed That The Contributory Factors For Antibiotic Resistance Were Mainly Due To Inadequate Dosage, Inaccurate Choice And Incomplete Treatment Of Antibiotics. 8 Out Of 10 Respondents Opined That It Is Necessary To Know About Antibiotic Resistance And Awareness Should Be Created Among The Public.

**Key Words:** Knowledge, Attitude, Practice, Antibiotic Resistance, Irrational Use

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### I. Introduction

WHO defines the appropriate use of antimicrobials as “the cost-effective use of antimicrobials which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance.” Antibiotic resistance (ABR) is one of the major health problems in developing countries like India where relatively easy availability and higher consumption of antibiotics (AB) leads to high level of ABR. India has the highest infectious disease burden in the world and consequently AB play a critical role in limiting morbidity and mortality.<sup>1</sup> Management of common and lethal bacterial infections has been critically compromised by the appearance and rapid spread of AB resistant bacteria. A recent report showed that irrational use of antimicrobial agents led to the increasing development of ABR.<sup>2</sup> Only the extent and

percentage of ABR varies from country to country but the underlying problem of resistance and misuse remains the same globally. Various approaches have been taken worldwide to meet the challenges which are posed by its spread. One of the approaches which is commonly suggested is to undertake instructional and educational campaigns among the general population<sup>3</sup> as well as among the health care personnel<sup>4</sup> regarding the steps which can limit its development and spread.<sup>5,6</sup> Prescribers have an important role to play in the battle against ABR, not only through their safe and rational prescribing, but also by promoting patient awareness and knowledge, and imparting health education to the community regarding safe medication practices. Various studies have described the inability of the prescribing physicians in creating awareness and providing adequate education to the patients regarding AB usage.<sup>3</sup> Young doctors should be given more education during their UG training regarding ABR and antibiotic prescribing. This is a crucial period during which the importance of these issues should be emphasized, because once the doctors are qualified, it is difficult to change their deeply entrenched views and behavior.<sup>7</sup> A better understanding of what the doctors know and believe about these issues of ABR and its usage can assist in planning an effective educational intervention for them. To the best of our knowledge there were no previous studies that analyzed the knowledge, attitude and practice of health care professionals on AB use in Manipur. Hence, this study was undertaken among junior doctors in order to assess their knowledge and attitude concerning ABR, as well as their self-reported practices in a tertiary care hospital.

## **II. Objectives**

1. To assess the knowledge, attitude of junior doctors about ABR and their self-reported practices related to AB usage
2. To determine the association between knowledge and attitude of ABR with variables of interest like gender, designation and age

## **III. Materials And Methods**

This was a cross-sectional study conducted among all the junior doctors (interns and junior residents) in RIMS, Imphal during 23<sup>rd</sup> Feb to 24<sup>th</sup> March '17. Those who were not willing to participate and those who could not be contacted after two visits. Sample size was not considered as we intended to cover all the junior doctors (interns and junior residents) in RIMS. The study instrument used to collect data consists of a pretested self-administered structured validated questionnaire from studies conducted in Congo by Threimer et al and in Kerala by Khan et al was used to collect data. The questionnaire consisted of the following 4 sections:

Part I: Socio-demographic profile

Part II: 1) Knowledge about antibiotic resistance

2) Attitude towards antibiotic resistance

3) Self-reported practice on antibiotic usage

12 close-ended questions were used to study the knowledge, 9 questions using a 5-point Likert scale, whose responses ranged from 'strongly agree' to 'strongly disagree' to assessed attitude, 5 questions using a 5-point Likert scale which ranged from 'always' to 'never' and 5 reasoning based questions were used to assess their self reported practices and 2 miscellaneous questions on the source of knowledge on AB and recommendations to prevent ABR was asked.

Data were collected from 27<sup>th</sup> Feb to 12<sup>th</sup> March, 2017. After explaining the purpose of the survey, an informed oral consent was taken from all the participants. The students were reassured about their anonymity and the importance of honest answer at the time of questionnaire administration. Instructions were given to them as to how to fill the questionnaire. The questionnaires among the Junior Residents and internees were distributed and collected the filled questionnaire on the same day.

**3.1 Statistical Analysis:** Data collected were checked for completeness and consistency. Data compilation and analysis was done using software SPSS 21 version. Descriptive statistics like mean (SD), percentages and Chi square test for testing the significance were used for analysis. A probability value of <0.05 was taken as significant.

**3.2 Operational Definition:** Practice of antibiotic usage was defined as the one who was taking any antibiotic in their life time due to illness. Indiscriminate use of antibiotic was defined as those who discontinued antibiotic after 2-3 doses when they felt better from illness.

**Knowledge score:** There were 10 close ended questions each questions carrying maximum score of 1 and minimum score of 0 and 2 multiple choice questions 1 score for each correct option for evaluating the knowledge about antibiotic resistance.

The maximum total score was 22 and minimum 0

Categorization was done as follows:

- 1) Inadequate knowledge - score obtained <13
- 2) Adequate knowledge - score obtained  $\geq$ 13

Since 13 is the median value of total desirable score 22

Attitude Score: There were 9 questions for evaluating the attitude about ABR using a 5-point Likert scale. Each questions carrying maximum score of 2 and minimum score of -2. The maximum obtainable score was 18 and minimum -18.

Categorization was done as follows:

- 1) Favorable Attitude- score obtained  $\geq 9$
- 2) Unfavorable Attitude- score obtained  $< 9$

Since minimum positive attitude score being 9

**3.3 Ethical issues:** Approval was obtained from the Research Ethics Board RIMS, Imphal before beginning the study. Informed verbal consent was taken from the participants and confidentiality was maintained.

#### IV. Results

Total number of junior doctors in RIMS during that time was 195. Of which number of junior doctors who responded were 167. More than half (55.1%) of the respondents were female.

Maximum of the respondents were MBBS interns (52.8%), then Dental interns (20.4%) and Junior Residents (16.8%).The response rate was 85.64%. Mean age of participants was  $24.5 \pm 1.43$  (SD) years; the minimum and maximum age being 21 and 30 years respectively.

**Table 1: Responses to “Indiscriminate and injudicious use of AB can lead to” (N=167)\***

RESPONSE	FREQUENCY	%
Ineffective treatment	133	79.6
Increased adverse effects	130	77.8
Exacerbation or Prolongation of illness	111	66.5
Emergence of bacterial resistance	159	95.2
Additional burden of medical cost to the patient	142	85

\*Multiple answers allowed

**Table 2: Responses to “Contributory factors for ABR”**

Response	Frequency	%
Use of AB for self-limited non bacterial infections	131	78.4
Use of AB with a broader than necessary spectrum	114	68.3
Use of AB for shorter / longer than standard duration	130	77.8
Inaccurate choice of AB	135	80.8
Inadequate dosage to the patient	143	85.6
Over prescription / overconsumption (Too many AB prescriptions)	117	70.1
Treatment not completed	133	79.6

**Table 3: Responses regarding knowledge towards AB usage**

Question	Overall answered correctly	%
1. A 4-year-old girl has diarrhoea for 4 days (3 stools /day). She has no fever at the time examination or during the last few days. Which treatment? a) amoxicillin b) TMP/SMX c) amoxicillin-clavulanic acid d) no AB treatment, only ORS e) don't know	137	82
2. A 6-year-old child has a fever of 38° C, purulent rhinitis and angina for 2 days. At inspection, the throat is reddish. Which treatment? a) TMP/SMX b) amoxicillin c) amoxicillin-clavulanic acid d) no antibiotic e) don't know	7	4.2
3. During your ward round, you see 2 pts with severe renal failure. Patient A is a 68-yr-old man suffering from serious cellulitis at the leg being treated with clindamycin. Patient B is a 64-yr-old diabetic woman being blindly (empirically) treated for septicemia with ceftriaxone. Dosage reduction is needed for: a) Patient A b) Patient B c) both d) in neither patient A nor patient B e) don't know	25	15
4. Which one of the following antibiotics is safe during pregnancy? a) amoxicillin b) ciprofloxacin c) gentamicin d) don't know	90	53.9
5. Which one of the following antibiotics has the best activity against anaerobes?	123	73.7

a) ciprofloxacin <b>b) metronidazole</b> c) cotrimoxazole d) don't know		
6. Methicillin resistant - Staphylococcus aureus is susceptible to: a) amoxicillin-clavulanic acid b) cefotaxime c) ceftriaxone <b>d) none</b> e) don't know	58	34.7
7. Which one of the following antibiotic most effectively crosses the blood-brain barrier? a) clindamycin <b>b) ceftriaxone</b> c) vancomycin d) don't know	49	29.3
8. Aminoglycosides such as gentamicin are very active if they are administered as follows- <b>a) orally three times daily b) parenteral once daily</b> c) parenteral three times daily d) Don't know	53	31.7
9. In India, what is according to your information the estimated resistance rate of Salmonella Typhi to Cotrimoxazole (Bactrim)? a) 0-10% b) 10-20% c) 25-50% <b>d) 50 - 75%</b> e) don't know	15	9
10. In India, what is according to your information the estimated resistance rate of Klebsiella to Ceftriaxone? <b>a) 0-10%</b> b) 10-20% c) 25-50% d) 50 - 75 % e) don't know	18	10.8

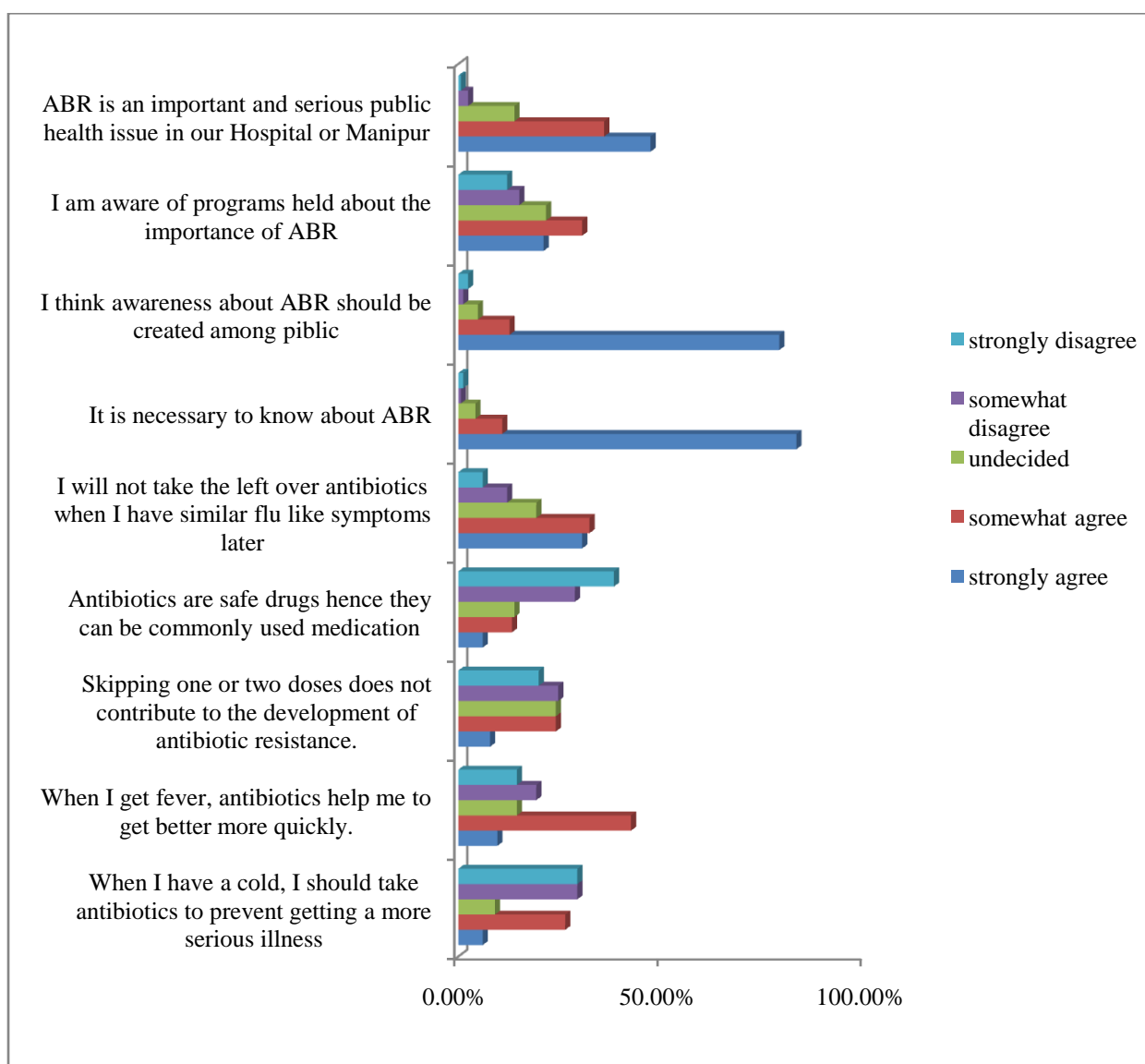


Fig. 4: Responses regarding attitude towards AB usage

Table 4: Responses to “How often do you prescribe AB?”

Prescription given	Frequency	%
Once daily or more	55	32.9
3 - 5 times per week	52	31.5
1 - 2 times per week	60	35.9

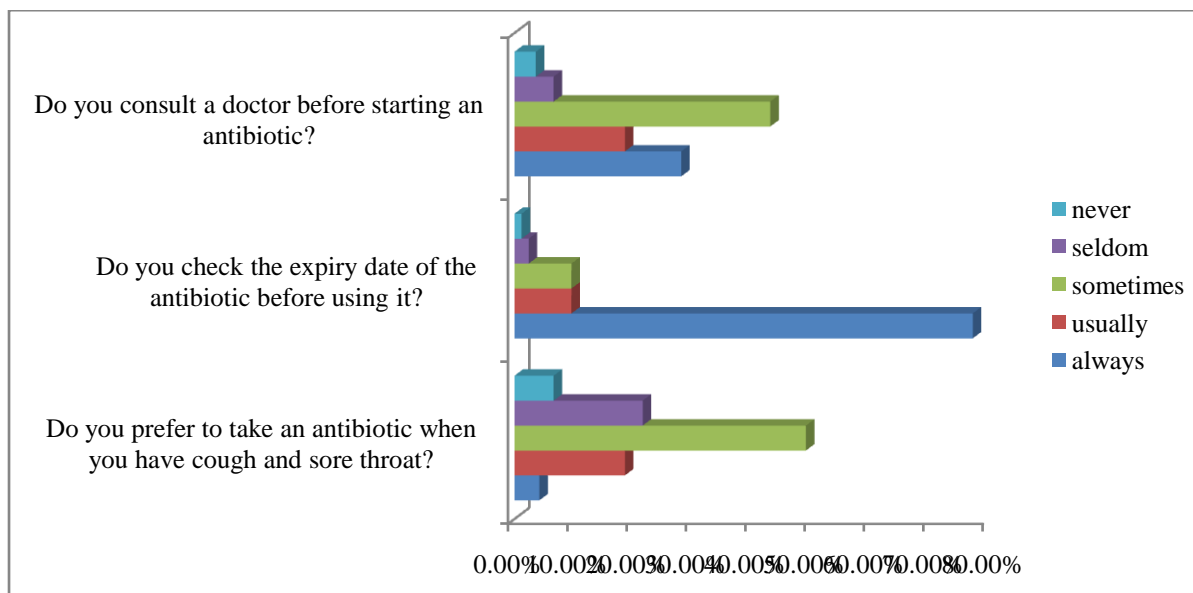


Fig.5: Responses regarding practice towards AB usage

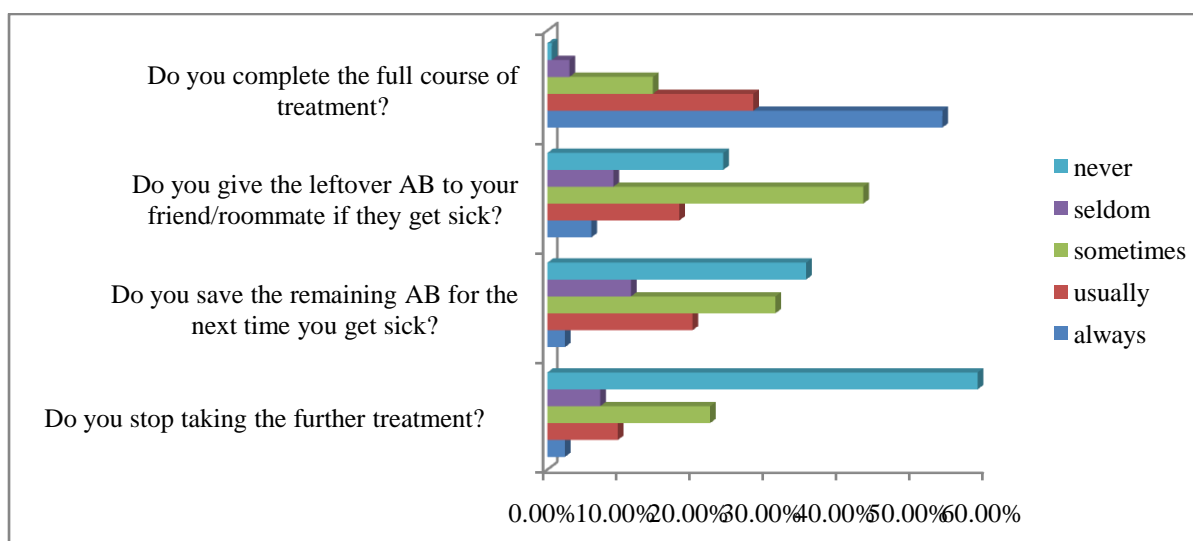


Fig. 6: Responses to “A doctor prescribes a course of AB for you. After taking 2–3 doses (incomplete course) you start feeling better.”

Table 5: Responses to “I have self medicated with AB. Because”

Reason	Frequency	%
Cost saving	14	18.4
Convenience	131	78.4
Others	22	13.2

Table 6: Responses to “I will increase the dose of AB during the course of treatment. Reason “

Reason	Frequency	%
Symptoms do not subside	110	65.8
To recover faster	29	17.4
Expiry date is nearer	5	3
Others	23	13.8

Table 7: Responses to “I will stop taking the prescribed AB during the course of treatment. Because”

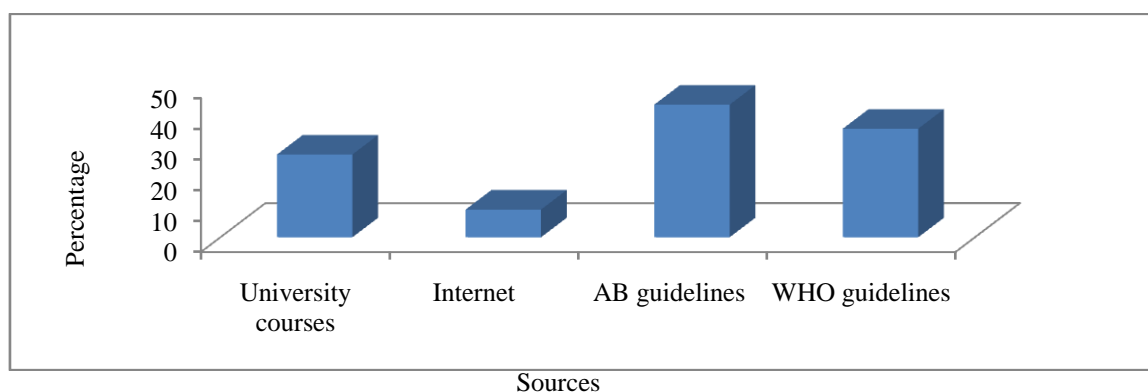
Reason	Frequency	%
Symptoms got better	29	17.4
Adverse reaction occurred	116	69.5
Others	22	13.1

**Table 8:** Responses to “If I get similar illness later, I will not consult a doctor and I will buy AB myself. Reason”

Reason	Frequency	%
I will buy AB on my own experience	47	28.1
I will ask opinion from relatives or friends	5	3
I will get from previous doctor prescription	80	47.9
I will get information from internet	5	3
Others	30	18

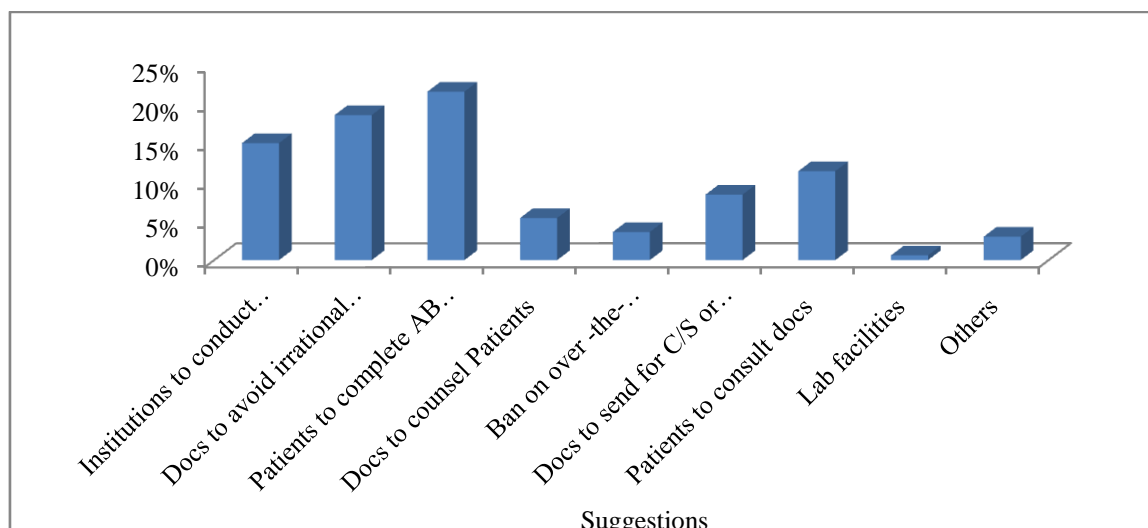
**Table 9:** I will switch to another antibiotic during the course of treatment. Reason

Reason	Frequency	%
The former did not work	115	68.9
The latter is one cheaper	5	3
To reduce adverse reaction	31	18.6
Others	16	9.5

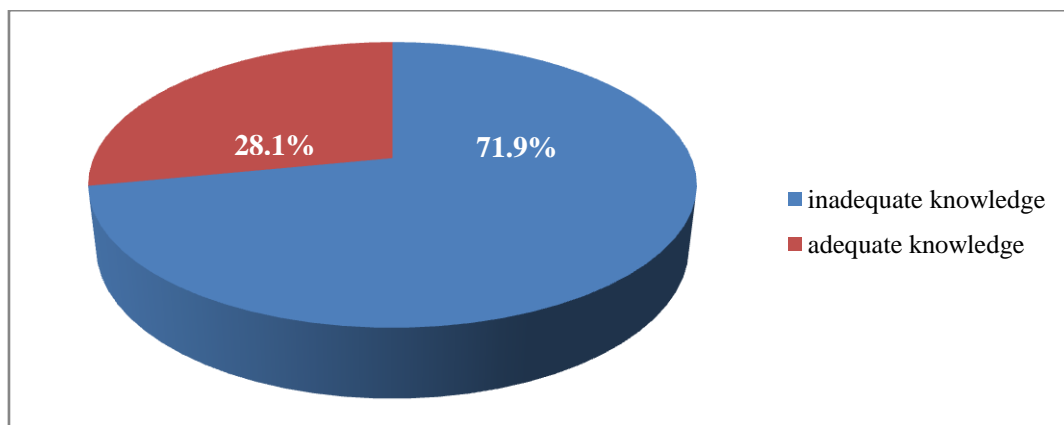


**Fig.7:** Responses to “Which of these sources influences your AB prescribing?”

Multiple answers allowed



**Fig. 8:** Recommendations to prevent ABR



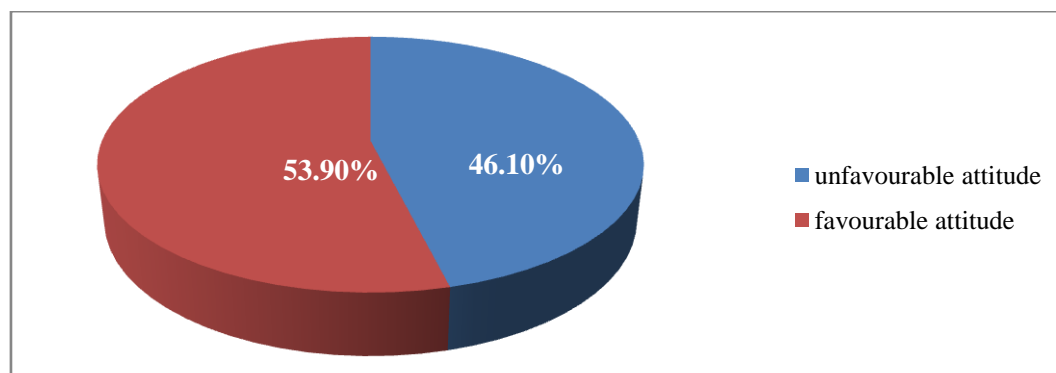
**Fig.9:** Distribution of participants by knowledge

Fig.9 shows that almost 3/4<sup>th</sup> of the junior doctors had inadequate knowledge regarding AB usage

**Table 11:** Association of knowledge with designation

Designation	Knowledge		p-value
	Adequate	Inadequate	
Interns	65 (46.8%)	45 (53.2%)	<b>0.003</b>
Junior Residents	23 (82.1%)	5 (17.9%)	

Table 11 shows that junior interns were significantly associated with more knowledge regarding antibiotic usage compared to interns



**Fig.10:** Showing respondents' attitude (N=167)

Fig 10 shows that a little more than half of the junior doctors had favorable (right) attitude towards antibiotic usage

**Table 14:** Association of attitude towards AB usage with age

Age(Yrs)	Attitude		p-value
	Favourable	Unfavourable	
<24	6 (15.8%)	32 (84.2%)	<b>0.002</b>
≥24	57 (44.2%)	72 (55.8%)	

Table 14 shows that junior doctors whose age was equal to or more than 24 years were significantly with more knowledge than those whose age was less than 24 years.

**Table 15:** Association of attitude towards AB usage with designation

Designation	Attitude		p-value
	Favourable	Unfavourable	
Interns	46 (33.1%)	93 (66.9%)	<b>0.006</b>
Junior Residents	17 (60.7%)	11 (39.3%)	

Table 15 shows that Junior Residents was significantly associated with having favorable(right) attitude towards antibiotic usage as compared to the attitude of the interns.

## V. Discussion

Our study provides useful information about the knowledge, attitudes, perceptions and the practices of junior doctors with respect to antibiotic resistance and usage, which may be utilized to plan suitable educational interventions that aim at improving the antimicrobial prescribing and use.

**Knowledge on AB prescribing:** In our study, 95.2% of the respondents agreed that indiscriminate use of AB lead to bacterial resistance which has a similar finding by some researchers Ying H et al, Akram A et al and Tarao et al.<sup>8,9,15</sup> A similar study conducted by Afzal Khan et al<sup>10</sup> also found that 85% of the students believed emergence of bacterial resistance was due to indiscriminate use of AB which was congruence to the finding of Manali Mahajan et al.<sup>11</sup> A study conducted by Faeze Keihanian et al<sup>12</sup> found 73.1% of them believed ABR was mainly due to indiscriminate use of AB. Contributory factors for ABR was inadequate dosage to patient(85.6), inaccurate choice of AB(80.8%) and not completion of treatment(79.6%).

The junior doctors has poor knowledge in upper respiratory tract infection, antibiotic susceptibility to MRSA, dosage adjustment in renal impairment, gentamycin prescription, treatment for meningitis, resistance rate of ceftriaxone and cotrimoxazole.

For the question on susceptibility of AB towards MRSA, Malaysian medical officers responded well as compared to our study and DR Congo study as well.<sup>19,13</sup> In West Indies of the United States, Tennant et al.<sup>15</sup> found that knowledge of resistance-prone antibiotic and specific organisms at University Hospital of West Indies was poor, except for methicillin-resistant *Staphylococcus aureus*.

The virulence of the organism, the risk of adverse effects and super infection as well as the immune status of the patient, were considered as the factors which deserved the most consideration before the prescription of an antibiotic. The ability of the antibiotic to promote resistance, the in-vitro antibiotic sensitivity of the causative organism and the pharmacokinetic profile of the antibiotic were given second priority. This demonstrates that the students were more aware and concerned about the individual patient's benefit and harm, the dangerous consequences which result to the society due the indiscriminate antibiotic use may not be obvious to them.

We also found that the knowledge about emergence of bacterial resistance following inappropriate use of AB was found to be better among junior residents than the interns which were statistically significant. This finding is in contrast to other studies in Congo also found out that there was no significant difference in the mean score of knowledge according to years of experience.<sup>13</sup> A study in France and Scotland by Pulcini C et al<sup>15</sup> revealed that knowledge of prevalence rate on ABR was also not influenced by past training experience. In John Hopkins Hospital, Srinivasan et al<sup>4</sup> found that there was no significant difference in knowledge score for various years of training. This significant finding implies that longer duration of practice does not ensure good knowledge on AB prescribing. Thus, appropriate training and update were required for all medical practitioners irrespective of their seniority in the institution. As analyzed in the other study, there was no statistical significant difference in years of service with regards to knowledge score.

**Attitude towards AB prescribing:** Almost half (47%) were not aware that ABR is a serious problem in Manipur. The low level of awareness on antibiotic resistance in own practice might be due to the fact that there was limited access to data on antibiotic resistance in their own local practice. A similar response was noted in previous studies, where most of the respondents underestimated the prevalence of the antibiotic resistance at their own institution.<sup>13</sup> Therefore, it is naturally befitting to encourage more data dissemination on local antibiotic resistance to prescribers as also highlighted by the Peru study.<sup>18</sup> The attitude of the study participants with regards to antibiotic use and resistance was found to be casual and lax. More than one-fourth (26%) of them reported that antibiotics should be taken on developing a cold and almost two-fifth (42.5%) of the junior doctors revealed that they somewhat agreed to take antibiotics when they get fever to get better more quickly. Such wrong beliefs may lead to inappropriately high rates of antibiotic consumption, which can result in a corresponding increase in the bacterial resistance. Almost 2 of 10 perceived that antibiotics are safe drugs hence they can be commonly used medication. These findings are consistent to the findings by Khan et al.<sup>10</sup> In our study, almost 1/4<sup>th</sup> (24%) of the junior doctors was undecided whether skipping one or two doses contribute to the development of antibiotic resistance. Age group 24 and above had more favourable (right) attitude than below 24 years which was statistically significant. Junior residents were having more favourable (right) attitude than the interns which was also found to be statistically significant.

**Practice in antibiotic prescribing:** More than half (58.70%) of our respondent never stop taking AB inspite of feeling better after 2-3 doses of AB, which was similar to the finding by Afzal Khan AK et al and Tarao et al (54.8%)<sup>10,15</sup> whereas a study done by Manali Mahajan and co-worker<sup>11</sup> found 87.3% of the respondent stop continuing the course of AB. In our study, only 32.9% consulted doctors, the rest self medicated themselves similarly to the study conducted by Tarao et al<sup>15</sup> in which 40.1% of the students consulted doctors before they start AB whereas more than 90% consulted doctors in a study conducted by other researchers.<sup>10,11</sup> This may be so because being trained as doctors themselves, they did not depend on specialists for consulting regarding usage of AB. Expiry date of the AB before taking was checked by only 77.20% which was lower to the finding



of Tarao et al<sup>15</sup> in which 94.4% of the students always checked the expiry date. The self reported practices of our study participants with regards to AB use were found to be unsatisfactory. Only a little more than half (53.9%) always completed the full course of the prescribed treatment. Overall, the frequency of AB prescribing among all three countries; Malaysia, DR Congo, and Peru was more than once daily.<sup>13,17</sup> which was similar to our study findings. High AB prescribing rate does not necessarily indicate irrational use as some antibiotic prescription was well justified.

When asked on sources of information pertaining to AB, a vast majority of respondents use AB guidelines followed by WHO guidelines, lectures and internet. University courses and lectures on AB was claimed as not so important point of reference. On the other hand, lectures were the most used training in Dundee and Nice.<sup>21</sup> Proactive action should be prompted to provide more courses and workshops to prescribers. It would be interesting with the idea of providing courses and workshops via the net are being done in developed countries.

One of the common misperceptions which is held by the prescribers while they treat their patients is that more is better, in treating the colonization rather than the infection or in using broad-spectrum antimicrobials. This falsely held belief is considered to be a primary barrier which prevents the development of ABR.<sup>22</sup>

Learning about the antimicrobial prescribing in pharmacology must be connected clearly with the infection control measures in microbiology. The significance of simple measures like hand hygiene in the control of resistance should be endorsed and its practice should be inculcated at an earlier stage of the medical education.

The students should be made aware of these important facts and a sense of responsibility should be nurtured, that as prescribers, they are not only responsible for the benefit and the welfare of their patients but also for the society at large. Outcome-based education is said to be an important tool in which the requirements are explicitly defined in detail, to ensure that the medical graduates are fit for practice. This can be utilized for educating the students about antibiotics, so that as prescribers, they are fit to prescribe AB, maximize their effective and efficient use and minimize the development of resistance.<sup>24</sup>

Apart from teaching about AB prescribing, the principles of the protocol development for AB use in health care facilities should form an integral part of the undergraduate teaching. Small group exercises that facilitate the students in practicing patient education skills such as negotiating with patients about the need for AB and educating them about the proper use of AB, should form an important part of the students' AB curriculum.<sup>25</sup> The medical education strategies should aim, not only to increase the knowledge, but also to change the behaviour and to improve the patient outcomes.<sup>26</sup>

Moreover, antibiotic resistance has been widely discussed and publicized in the press, media and on the online discussion forums and the general public are becoming knowledgeable about the issue of resistance. Since the media and the internet have become important sources of information, especially among the youth, they have become the medium of gaining knowledge and awareness regarding various public issues.

Our study provides an important insight regarding their knowledge, attitudes, perceptions and practices, which can be considered, in order to plan for an effective undergraduate curriculum regarding antibiotic resistance and usage.

### **5.1 Strengths**

Good response rate (85.64%). Use of validated questionnaire as a study tool in our study. Possibly one of the first study conducted in Manipur among the junior doctors to assess the KAP of antibiotic resistance and usage

**5.2 Limitation** Post Graduates were not included in the study. If included the study would have receive wider perspectives on this topic.

## **VI. Conclusion**

7 out of 10 junior doctors had poor knowledge of antibiotic resistance and its usage.

Only half of the junior doctors had favorable attitude towards antibiotic resistance.

8 out of 10 junior doctors revealed that the contributory factors for antibiotic resistance were mainly due to inadequate dosage, inaccurate choice and incomplete treatment of antibiotics.

8 out of 10 respondents opined that it is necessary to know about antibiotic resistance and awareness should be created among the public. Nearly one-fifth of the junior doctors recommended that doctors should avoid irrational antibiotic prescription, more than one-fifth of them suggested that patients should complete their treatment course and 2 out of 10 of them suggested the need for CME on antibiotic resistance and its usage. Resident doctors were found to have more knowledge on antibiotic resistance as well as having better attitude towards antibiotic use than the internees and were found to be statistically significant.

## VII. Recommendation

Our study provides an important insight regarding the knowledge, attitudes, and self-practices regarding antibiotic resistance and usage among the future doctors, which can be considered, in order to plan for an effective undergraduate curriculum. Periodical CME programs on ABR and antibiotic usage should be made compulsory for all junior doctors.

## Acknowledgement

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**Conflict of Interest** The authors declare no competing interests.

**Author's Contribution** ZMS and BSA, conceived the research work. ZMS and TN coordinated the data collection. ZMS, VV, V and DL carried out the data analysis. ZMS and TN contributed in literature review. ZMS wrote the draft of manuscript. BSA interpret the results and revised the manuscript. All the authors contributed in the revision of the paper and agreed on the final manuscript.

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