Disease and Health Research – New Insights Vol. 1 – ebook

Chapter · February 2025

DOI: 10.9734/IJTDH/2023/v44i231499

3 authors:

Kiiza Stephen
Bugema University
17 PUBLICATIONS **6** CITATIONS
SEE PROFILE

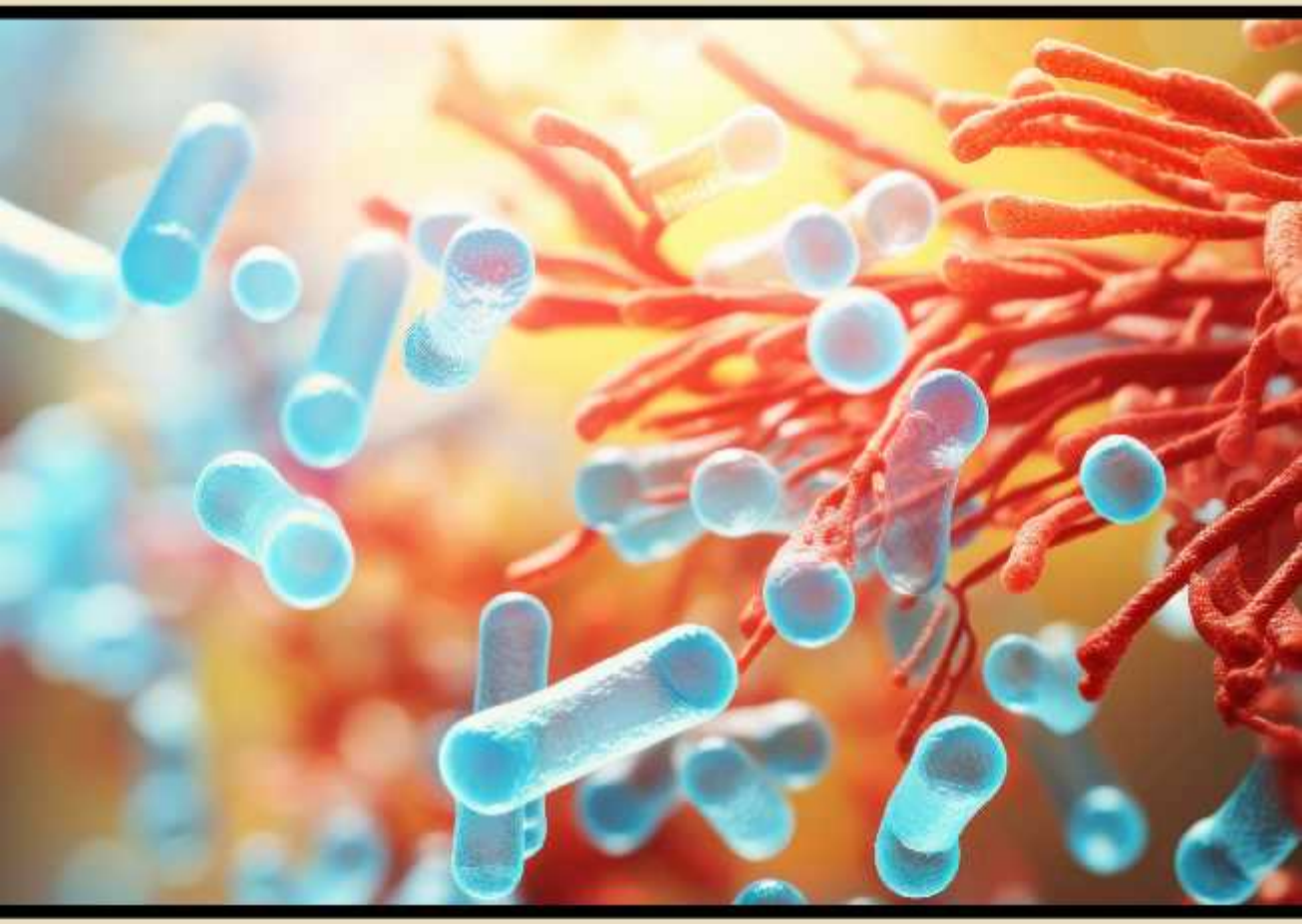
Christopher Ddamulira
The Uganda National Council for Science and Technology
36 PUBLICATIONS **69** CITATIONS
SEE PROFILE

David Robinson Mutekanga
Bugema University
32 PUBLICATIONS **1,223** CITATIONS
SEE PROFILE

Disease and Health Research - New Insights

Vol. 1

Edited by Dr. Giou-Teng, Yiang



B P International

Disease and Health Research - New Insights

Vol. 1

Disease and Health Research - New Insights

Vol. 1

India ▪ United Kingdom

B P International

Editor(s)

Dr. Giou-Teng, Yiang
Tzu Chi University, Taiwan, R.O.C.

FIRST EDITION 2024

ISBN 978-81-976653-0-1 (Print)
ISBN 978-81-976653-1-8 (eBook)
DOI: https://doi.org/10.9734/bpi/dhrni/v1

Peer-Review Policy: Advanced Open Peer Review policy has been followed for review. All manuscripts are thoroughly checked to prevent plagiarism. As per editorial policy, a minimum two peer-reviewers reviewed each manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication.

Chapter 8
Approved by
(1) Prof. S. Venkatesan, India Institute of Speech & Hearing, India.
Reviewers
(1) Asif Ali Amir Ali Khowaja, College of Physicians and Surgeons, Pakistan.
(2) Gauri Shankar Pandit, Zulfiqar Ali Bhutto Medical University, Pakistan.
(3) Richa Arora, Bihar Animal Sciences University, India.

Chapter 9
Approved by
(1) Dr. Muhammad Akram, University Faisalabad., Pakistan.
Reviewers
(1) Anantha Krishna B S, India.
(2) P. Suresh, Sri Venkateshwaraa Medical College Hospital and Research Centre, India.

Chapter 10
Approved by
(1) Dr. Rameshwari Thakur, Muzaffarnagar Medical College, India.
Reviewers
(1) Sahar Mohamed Mahdy Omar, Ain Shams University & Galala University, Egypt.
(2) Ehimen Ferguson, Spas Research Centre and Consultancy Services, United Kingdom.
(3) Santoshi Ram Ghodake, SMBT Dental college and Hospital, India.

Chapter 11
Approved by
(1) Dr. Chan-Min Liu, Xuzhou Normal University, PR China.
Reviewers
(1) Joseph O. Ashaolu, Redeemer's University, Nigeria.
(2) Shruti D Nayak, Yenepoya University, India.

Chapter 12
Approved by
(1) Dr. Elvira Bormusov, The Lloyd Rigler Sleep Apnea Research Laboratory, Israel.
Reviewers
(1) Manuel de Jesús Verdecia Tamayo, University of Granma, Cuba.
(2) Jack Ogony, Jomo kenyatta University of Agriculture and Technology, Kenya.

Chapter 13
Approved by
(1) Dr. Malar Kodi S., All India Institutes of Medical Sciences, India.
Reviewers
(1) Wingston Ng'ambi, University of Malawi, Lilongwe, Malawi.
(2) Parastoo Amiri, Sabzevar University of Medical Sciences, Iran.

Chapter 14
Approved by
(1) Dr. Muhammad Akram, Government College University Faisalabad, Pakistan.
Reviewers
(1) Anatolii Tsarkov, University of Zambia, Zambia.
(2) Zambia, UNZA – University of Zambia, Zambia.
(3) Nur Aifiah Binti Ibrahim, Universiti Teknologi MARA, Malaysia.

Contents

ABOUT THE EDITOR

Prof. Giou-Teng, Yiang
Tzu Chi University, Taiwan, R.O.C.

He is currently the member of Academic Committee of Taiwan Society of Emergency & Critical Care Medicine (TSECCM) and the member of Academic Committee and Professional Training Committee of Taiwan Society of Emergency Medicine. He is currently working as Director of Emergent Department at the Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation from 2011 to the present. He received his Ph.D. degree in Medical Sciences in 2009 from the Tzu Chi University, Hualien, Taiwan. He is currently the Director and Associate Professor at Department of Emergency Medicine from 2013 to the present, Deputy Head of Department of Medicine, School of Medicine, Tzu Chi University, Hualien, Taiwan, from 2018 to the present.

He is not only specialized as an emergency physician, He is also the instructors of Advanced Cardiac Life Support (ACLS), Emergency Trauma Training Course (ETTC), Advanced Pediatric Life support (APLS). He has more than 70 publications of original articles, case reports, and review papers being published in peer review journals covering research fields of Emergency and Critical Care Medicine, Trauma and Basic Sciences. He is the reviewers of many international journal, and guest editor of B P International.

PREFACE

This book covers key areas of disease and health research. The contributions by the authors include post covid vaccination parsonage-turner syndrome, COVID-19, neuralgic amyotrophy, sars-cov-2 vaccines, acquired peripheral neuropathy, neuropathic pain, sezary syndrome, mycosis fungoides, flowcytometry, skin lesions, EORTC staging, immunophenotypic pattern, lymphomas, acute myeloid leukaemia, malignant clonal disorder, cytogenetics, febrile illnesses, malaria fever, pregnancy, treatment seeking behavior, malaria vaccine, antibodies, infectious illness, serum creatinine, hypertension, adolescent, organ function, systolic and diastolic blood pressure, hematological indice, pediatric population; physical fitness, cardiorespiratory, muscular endurance, cardiovascular fitness, fitness gram test, skeletal health, acute pancreatitis, glasgow score index, BISAP scoring, mortality, virus hemorrhagic fevers, community-acquired pneumonia, acute zoonotic diseases, lymphocytic choriomeningitis virus, obesity, non-communicable diseases, body mass index, malnutrition, free maternal health care policy, national health insurance scheme, antenatal care, early neonatal mortality, antibiotic therapy, respiratory atopy, allergic diseases, T helper immune response, attention deficit hyperactive disorder, behavioral strategies, cognitive behavioral therapy, pharmacologic treatment, preventive methods against mosquito bite, awareness, vector-borne diseases, disease control program. This book contains various materials suitable for students, researchers and academicians in the field of disease and health.

Chapter 1
Print ISBN: 978-81-976653-0-1, eBook ISBN: 978-81-976653-1-8

Prevalence of Hypertension Disorders among Adolescent Students in Ghana

Abena Sekyere [a*]

DOI: https://doi.org/10.9734/bpi/dhrni/v1/909

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/909

ABSTRACT

Aims: The main purpose of this study is to investigate the prevalence of hypertension, associated risk factors, and its effect on physical activity in young people aged 14-19 years.
Study Design: This is a Cross-sectional study.
Place and Duration of Study: Sample: Department of Biochemistry, College of Science, Kwame Nkrumah University of Science and Technology between June 2009 and July 2023.
Methodology: A multistage sampling method was used to select 909 youth from three secondary schools (three towns in the Ashanti region of Ghana). The follow-up study was conducted on 142 people with high blood pressure. Anthropometric and blood pressure were measured with approved devices. Measurement of physical activity and dietary intake via survey. Blood pressure was measured using a validated automatic sphygmomanometer, with participants seated comfortably and resting for at least five minutes before measurement. Three readings were taken at one-minute intervals, and the average of the last two was recorded to reduce the impact of stress or short-term changes. Systolic and diastolic blood pressures were the main parameters recorded. Additionally, the study evaluated cardiovascular parameters (heart rate, echocardiography, ECG) and renal parameters (serum creatinine, GFR, urinalysis, BUN).
Results: Research shows that the prevalence of high blood pressure is 9.1% and the incidence of prehypertension is 24.8%. The prevalence of high blood pressure is significant by school choice. A majority of men have higher blood pressure than women, with 10.6% having high blood pressure, 46.6% having prehypertension, and 42.6% having high blood pressure. Data shows that 81.6% of participating parents are self-employed. The results show that there is little work, 72.73% of hypertensive patients are not working, while 40.32% and

[a] *Department of Biochemistry, College of Science, Kwame Nkrumah University of Science and Technology, Ghana.*
**Corresponding author: E-mail: abenasekyere@yahoo.co.uk;*

59.97% of inactive and hypertensive patients are still sedentary. The results showed that MCV was negatively correlated with systolic blood pressure and diastolic blood pressure (r=-0.230, r=-0.183), while MCHC was negatively correlated with systolic blood pressure and diastolic blood pressure (r = 0.171). showed., r = 0.256). RDW-SD was found to be negatively associated with systolic and diastolic blood pressure. There was a negative correlation between P-LCR and systolic and diastolic blood pressure (r=-.185, r=-.167).
Conclusion: The research found that blood pressure distribution varied among students in different schools, with the highest levels in KASS (57% hypertensive) compared to KOSS (19%) and BONWIRE (7%) (X^2 = 32.993, df = 4, p < 0.001). Despite examining cultural and lifestyle factors, no significant determinants of hypertension were identified. Lipid analysis also showed no significant differences between blood pressure groups. These findings highlight the need for further research to explore other potential causes of high blood pressure and to develop effective prevention and management strategies.

Keywords: Hypertension; adolescent; organ function; pre-hypertension; prevalence; normotensives; blood pressure; systolic; diastolic blood pressure; adolescent; hematological indice.

1. INTRODUCTION

Hypertension, which causes increased blood pressure, is recognized as a major health problem worldwide, affecting people of various age groups and demographic backgrounds [1]. Hypertension can cause cardiovascular diseases such as ischemic heart disease, left ventricular hypertrophy, pathological vascular changes and renal failure [2]. It is also thought to be associated with an increased risk of chronic kidney disease, cerebrovascular disease, and insulin resistance. The hazard ratio for men and women is 1.41 for cerebrovascular disease and 2.0 for heart disease [3,4]. As a result, heart diseases are thought to be responsible for the deaths of approximately 16.7 million adults in developed and developing countries. This number is expected to reach approximately 23 million in 2030, with a growth rate of 37.72% [5]. This situation shows the danger of high blood pressure in young people [6]. Carney et al. [7] described this disease as a public health threat. Data show that approximately 1 billion adults worldwide had high blood pressure in 2000. Although traditionally associated with the elderly, recent research has demonstrated the danger of high blood pressure in young people, raising concerns about long-term clean drinking health and prevention and management strategies [8]. Factors such as urbanization, changing diets, and sedentary lifestyles have been linked to the rise of youth in Ghanaian communities [9]. The literature is particularly interesting on the prevalence and determinants of serious illness among youth in Ghana. Understanding these health effects and their associated risks is important to inform intervention plans and strategic plans to clear the cardiovascular systems of these frail individuals. Lifestyle and nutritional factors in the development of hypertension in young adults. For example, Addo et al. [10] highlighted the impact of urbanization and dietary changes on the prevalence of hypertension in Ghana. Similarly, Ofori-Asenso and Garcia's [9] findings demonstrate the role of

negative behaviors and unhealthy eating patterns in the development of violence among boys and girls in low- and middle-income countries. This study presents various methods of youth mental health prevention and intervention in Ghana. The prevalence of hypertension disorders among adolescent students in Ghana is a growing public health concern. Recent studies indicate a significant occurrence of these disorders within this demographic. For instance, a study conducted by Laar et al. [11] revealed that approximately 15% of adolescent students in urban Ghanaian schools are affected by hypertension. This increased risk has been attributed to factors such as malnutrition, lack of physical activity, and increasing obesity among young people [11]. Additionally, Owusu et al. [12] pointed out that health-related conflicts and lack of interest in health services lead to an increase in violence in this age group, especially in rural areas [12]. These findings highlight the need for targeted interventions and policies to address the increasing prevalence of hypertension among youth in Ghana, with a focus on promoting healthy lifestyles and improving access to healthcare. and a review of solutions designed to address the underlying causes of hypertension while promoting cardiovascular disease among Ghanaian youth.

2. MATERIALS AND METHODS

This study was conducted in our secondary school in our town/city in the Ashanti region of Ghana. Bonwire SHS (BOSS) in Ejisu-Juaben District, Konongo Odumase SHS (KOSS) in Asante Akim Central District and Anglican SHS (KASS) in Kumasi City. The total number of students is 7,036. These include 3246 patients in KASS, 2803 patients in KOSS, and 887 patients in BOSS. This study used the "Cochrane" formula to calculate the sample size as 313, but most students agreed. A sample of 909 students was selected for pretesting in October 2016. Students whose blood pressure measurement was ≤120/80 mmHg were examined again in March 2017 to determine the prevalence of hypertension and related factors. Blood pressure was measured using an automatic sphygmomanometer that has been validated in large studies for its consistency and ease of use. Participants sit comfortably with their back on the floor, feet flat on the floor, and arms supported at the heart. To eliminate the effects of physical activity or stress on blood pressure measurements, ask students to rest for at least five minutes before taking the measurement. The measurement procedure involved three readings at one-minute intervals; The average of the last two measurements was recorded as the participant's blood pressure. This approach helps reduce the impact of stressful situations or short-term changes in blood pressure. Systolic and diastolic blood pressure are the main parameters recorded. Systolic blood pressure (SBP) is the pressure in the arteries when the heart beats, while diastolic blood pressure (DBP) is the pressure when the heart is between beats. In this study, cardiovascular parameters including heart rate, echocardiography, and electrocardiogram (ECG), as well as renal parameters such as serum creatinine, glomerular filtration rate (GFR), urinalysis, and blood urea nitrogen (BUN), were evaluated.

The number of students divided into the three levels of SHS is shown in Table 1.

Table 1. Participants selected for screening

Screening/School	Anglican SHS	Konongo SHS	Bonwire SHS	Total
First Screening	376	342	191	909
Rescreened	60	62	20	142

Source: Author's Construct, 2017

At baseline, 204 participants had blood pressure above 120/80 mmHg, but 142 agreed to participate in the study. Data collected from screening, including demographic characteristics, blood pressure, blood samples for biochemical analysis, nutritional status, and anthropometric data, were analyzed using IBM SPSS 22.0 (Chicago). While the mean and standard deviation are calculated for continuous variables, percentages are calculated for categorical variables. Significant differences in categorical variables were determined by the chi-square test, and the significance of the scores was determined by the t test. A p-value below 0.05 was considered significant.

3. RESULTS AND DISCUSSION

3.1 Prevalence of Hypertension among SHS Students

Majority of the students, 601 (66.10%) were classified as normotensive, based on their blood pressure. Students from KOSS had the highest prevalence followed by KASS and BOSS. There were significant differences ($p < 0.05$) in the BP of the students of the 3 schools (Table 1).

From the data it is possible to see the distribution of blood pressure among students in different schools. For example, in KOSS, 19% of students were classified as hypertensive, 82% were classified as prehypertensive, and 241 of 342 students were normotensive. Likewise, in KASS, 57% of students were hypertensive, 82% were prehypertensive, and 237 out of 376 students were hypotensive. By comparison, in BONWIRE, only 7% of students were hypertensive, 61% were prehypertensive, and 123 of 191 students were hypotensive. X^2) shows that there is a significant relationship between the distribution of blood pressure groups and the school the students attend ($X^2 = 32.993$, $df = 4$, $p < 0.001$). This suggests that the difference in blood pressure distribution between schools may not be due to risk factors. The higher proportion of hypertensive and prehypertensive students in KASS compared to KOSS and BONWIRE warrants further investigation into the following differences. Important factors to investigate include differences in sociodemographic characteristics, lifestyle behaviors, and school interventions. Sexuality precautions promote heart disease and prevent high blood pressure among college students. Strategies may include implementing health education programs in schools that promote healthy lifestyles, such as regular physical activity and healthy eating, and providing blood pressure screening and early intervention.

Table 2. Distribution of blood pressure among KOSS, KASS and Bonwire students

SHS Students	Blood Pressure Groups			Total	X^2	df	P-value
	Hypertensive	Pre-hypertensive	Normotensive				
KOSS	19	82	241	342			
(%)	5.60	24.00	70.50	100			
KASS	57	82	237	376			
(%)	15.20	21.80	63.00	100	32.993	4	0.000
BOSS	7	61	123	191			
(%)	3.70	31.90	64.40	100			
Total	83	225	601	909			
	9.10	24.80	66.10	100			

Table 3. Socio-demographic distribution of participants

Parameter	Normotensive n (%)	Pre-hypertensive n (%)	Hypertensive n (%)	% Total n (%)	P value
1. Gender					
Male	32 (42.6)	35 (46.6)	8 (10.6)	75(52.8)	
Female	37 (55.2)	27 (40.3)	3 (4.5)	67(47.1)	0.20
2. Mothers occupation					
Civil servant	3 (50.0)	3 (50.0)	0 (0.0)	6 (4.2)	
Public Servant	7 (46.6)	7 (46.6)	1 (6.6)	15 (10.5)	
Unemployed	1 (20.0)	3 (60.0)	1 (20.0)	5 (3.5)	
Self employed	58 (50.0)	49 (42.2)	9 (7.7)	116(81.6)	0.83
3. Fathers occupation					
Civil Servant	11 (47.8)	9 (39.1)	3 (13.0)	23 (16.2)	
Public Servant	11 (47.8)	10 (43.4)	2 (8.7)	23 (16.2)	
Unemployed	2 (50.0)	2 (50.0)	0 (0.0)	4 (2.8)	
Self employed	45 (48.9)	41 (44.5)	6 (6.5)	92 (64.7)	0.95

The age, waist circumference, BMI, body fat, muscle mass and visceral fat were determined and evaluated for their correlation with the hypertensive status of the participants. The ages of the participants who were categorized as hypertensive were averagely 17.91±1.14 years with that of the pre-hypertensive participants being 17.45±1.71, followed by the normal participants being 17.12±1.39 in a decreasing order, though the difference is not statistically significant at p>0.05. The waist circumference was averagely about 74 cm and not statistically significant (p>0.05). The BMI recorded no significant differences between the groups. The hypertensive class recorded BMI of averagely 20.66±6.99, followed by the pre-hypertensive and the normotensive group recording 18.88±8.56, which is the least.

Muscle mass and visceral fat measurements also followed same pattern with the hypertensive class recording the highest and the normotensives recording the least but the differences not being statistically significant (Table 3).

Table 4. Age, anthropometric and body composition of normotensive, pre-hypertensive and hypertensives

Parameter	Normotensive	Pre-hypertensive	Hypertensive	p-value
Age (years)	17.12±1.39	17.45±1.71	17.91±1.14	0.461
WC (cm)	74.42±8.09	74.18±7.50	74.27±7.72	0.450
BMI	18.88±8.56	20.02±7.41	20.66±6.99	0.847
Body Fat (%)	23.88±12.60	22.07±12.72	20.79±12.42	0.501
Muscle mass (%)	36.46±8.10	36.75±8.39	39.14±8.52	0.416
Visceral Fat	1.43±1.87	1.66±2.13	2.73±1.90	0.195

Values are Means±SEM

Regarding age, the mean age for hypertensive patients appears to increase slightly from normotensive to prehypertensive; hypertensive patients had the highest age (17.91 years). However, the age difference between the groups was not significant ($p = 0.461$). This suggests that age may not be an important predictor of blood pressure in this population. Blood pressure in three groups ($p>0.05$ for each group). This means that traditional measures of adiposity and adiposity may not be strong predictors of hypertension among young adults in this study population. There was a difference between the percentage of prehypertensive and prehypertensive patients, but this difference was not significant ($p = 0.416$). This finding challenges the suggestion regarding the relationship between muscle mass and hypertension risk and requires further investigation of the underlying mechanisms. There is no significant upward trend. Although not statistically significant, this difference suggests a relationship between arterial steatosis and hypertension risk in young students and requires further investigation in future studies (Table 4).

The blood pressure class of the participants had no significant effect on the lipid profile (HDL, LDL, Tchol and Trig) ($p>0.05$). Hypertensive patients recorded the highest mean levels of HDL (1.65 ± 0.06 mmol/L), LDL (1.90 ± 0.18 mmol/L) and

Tchol (4.02 ± 0.20 mmol/L), while Trig (1.02 ± 0.04 mmol/L), among the pre-hypertensive students collected, students with high blood pressure and high blood pressure had the lowest LDL value (1.73±0.08 mmol/L), and students with high blood pressure had the lowest Tchol value (1.02 ± 0.04 mmol/L). 3.83±0.12 mmol/L). Additionally, hypertensive students recorded the lowest TG (0.89 ± 0.06 mmol/L), whereas prehypertensive and normotensive students recorded the lowest HDL (1.60 ± 0.03 mmol/L) (Table 5).

Table 5. Physical activity profile of participants and hypertension status

Physical activity	Normotensive n (%)	Pre-hypertensive n (%)	Hypertensive n (%)	P-value
None	40(57.97)	25(40.32)	8(72.73)	
Once per week	3(4.35)	8(12.90)	1(9.09)	
Twice weekly	12(17.39)	16(25.81)	1(9.09)	0.045
Thrice	7(10.14)	6(9.68)	1(9.09)	
Four times per week	7(10.14)	6(9.68)	0(0)	
Five times per week	0(0)	1(1.6)	0(0)	
Total	69 (100)	62 (100)	11 (100)	

Table 6. Comparison of lipid profile of respondents on different blood pressure ratings

Blood Pressure Rating	HDL (mmol/L)	LDL (mmol/L)	TCHOL (mmol/L)	TG (mmol/L)
Normotensive	1.60±0.03	1.73±0.08	3.97±0.18	0.97±0.04
Pre-hypertensive	1.60±0.03	1.73±0.11	3.83±0.12	1.02±0.04
Hypertensive	1.65±0.06	1.90±0.18	4.02±0.20	0.89±0.06
F-ratio	0.252	0.264	0.269	0.971
Df	2	2	2	2
P-value	**0.777**	**0.768**	**0.765**	**0.381**

The values are Means ± S.D.

Table 6 compares lipid parameters in individuals with different blood pressures classified as normotensive, prehypertensive and hypertensive. Lipid parameters include high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TCHOL), and triglycerides (TG). No differences were found in HDL, LDL, TCHOL or TG levels (all $p>0.05$). This shows that the lipid index of the participants in this study cannot change much depending on the blood pressure. Little change was observed in some parameters. For example, the hypertensive group appeared to have slightly higher HDL levels compared to the normotensive and prehypertensive groups, but this difference was not significant ($p = 0.777$). Similarly, LDL and TCHOL levels increased slightly in the hypertensive group,

but these differences were not significant (p = 0.768 and p = 0.765, respectively). level (TG) showed a significant difference in the hypertensive group compared to the normotensive and prehypertensive groups, but this difference was not significant (p = 0.381). This finding contradicts the conventional belief that hypertension is associated with dyslipidemia, including high triglyceride levels. The measurements will have nothing to do with blood pressure. Although some lipids showed little difference from blood pressure, these differences did not reach significance. Factors other than blood lipids, such as genetic predispositions, lifestyle and metabolic factors, may also play an important role in determining the response to high blood pressure. Long-term follow-up to assess hypertension risk interactions, consideration of the potential for confounding variables, and changes in lipids over time associated with hypertension. Additionally, larger samples and more diverse studies will be needed to determine the relationship between lipid profile and hypertension in young people.

3.5 Comparison of Mean Macronutrient and Micronutrient Intake of Participants

Protein, total fat, carbohydrate, fiber, calcium, phosphorus, potassium and sodium had no significant effect on participants' blood pressure (p > 0.05). In normotensive students, the highest mean values were for protein (47.29±2.5 g) and sodium (3180.31±175.1 mg), while the highest mean values were for total fat (51.97±9.8 g) and carbohydrates (3180.31±175.1 mg). 322.48±61.5) was recorded for Students collected calcium (301.92 ± 68.9 mg), fiber (22.08 ± 4.6 g), and phosphorus (935.96 ± 155.6 mg). Prehypertensive students recorded the best potassium value (3615.32 ± 1952.0 mg).

Students with prehypertension have the lowest levels of protein (45.38±3.0g), total fat (46.07±3.2g), carbohydrates (263.55±17.1g) and phosphorus (when they have high blood pressure). 867.95±57.7 mg) Calcium (301.92 ± 68.9 mg), potassium (1884.84 ± 280.4 mg) and sodium (2777.88 ± 611.2 mg) are the least. Additionally, inactive students recorded the lowest amount of fiber (20.47 ± 1.5 g).

4. CONCLUSION

The research concluded that blood pressure distribution varied among students in different schools, with the highest levels observed in KASS. For instance, 57% of students in KASS were hypertensive compared to 19% in KOSS and 7% in BONWIRE ($X^2 = 32.993$, df = 4, $p < 0.001$). Despite examining various cultural and lifestyle factors, no significant determinants of hypertension were identified. Lipid analysis also showed no significant differences between blood pressure groups. These findings indicate the need for further research to explore other potential causes of high blood pressure in this population and to develop effective prevention and management strategies. These findings suggest that further research is needed to investigate other potential causes of high blood pressure in this population and to develop prevention and management strategies.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

All participants (909) of this study signed an informed consent form, in accordance to the CHRPE regulations, before answering the questionnaire and taking blood samples.

ETHICAL APPROVAL

Ethical clearance for the study was obtained from the Committee on Human Research Publication and Ethics (CHRPE) of the School of Medical Sciences, KNUST, Kumasi (CHRPE/AP/491/16) and consent was sought from the selected schools.

ACKNOWLEDGEMENTS

I am grateful to the Almighty God for seeing me through this course. My gratitude goes to my supervisor, Dr. Christopher Larbie who has been so much helpful in the write- up of this thesis. I am also thankful to Dr. Patricia Brown for her pieces of advice which also helped me a lot. A very big thank you also goes to my colleague Cynthia Asante who helped in diverse ways. I also wish for God's blessings for Sandra Boakye Yiadom, Nana Ama Amaniapong, Tracy Bonsu, Asamoah Detsi, Daniel Boakye, Kwadwo Agyemang and all who assisted me in the data collection. I am also indebted to my dear mother who supported me in the house. Thank you all and God bless you.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. World Health Organization. Hypertension; 2020. Available:https://www.who.int/news-room/fact-sheets/detail/hypertension
2. Sanchez RG, Labarathe DR, Forthofer RN, Fernandez Cruz A. National standard of blood pressure of children and adolescents in Spain: International comparison. Int J Epidemiol. 1992;21:478-487.
3. Arima H, Murakami Y, Lam TH. Effects of prehypertension and hypertension subtype on cardiovascular disease in the Asia-Pacific Region. Hypertension. 2012;59:1118-1123.
4. Lee M, Saver JL, Chang B. Presence of baseline pre-hypertension and risk of incident stroke: A meta- analysis. Neurology. 2011;77:1330-1337.

5. World Health Organization. World health statistics. Geneva: World Health Organization; 2012. Available:www.who.int/gho/publications/world_health_statistics/2012/accssed on 12/10/2016
6. Hajjar I, Kitchen TA. Trends in prevalence awareness, treatment, and control of hypertension in the United States 1986-2000. JAMA. 2003;298(10):206-290.
7. Kaerney PM, Whelton M, Reynolds SK, Muntner P, Whelton PK, He J. Global burden of hypertension: Analysis of worldwide data. Lancet. 2005;365:217-223.
8. Chiolero A, Paradis G, Paccaud F. The pseudo-high-risk prevention strategy. Hypertension. 2018;72(1):23-25.
9. Ofori-Asenso R, Garcia D. Cardiovascular diseases in Ghana within the context of globalization. Cardiovascular Diagnosis and Therapy. 2016;6(1):67-77.
10. Addo J, Agyemang C, Smeeth L, de-Graft Aikins A. A review of population-based studies on hypertension in Ghana. Ghana Medical Journal. 2017;45(2):3-16.
11. Laar A, Aryeetey R, Akweongo P. Prevalence of hypertension among adolescent students in urban Ghana. Journal of Public Health Research. 2023;12(1):45-52.
12. Owusu D, Osei A, Aikins M. Socio-economic factors and hypertension in rural Ghanaian adolescents. African Health Sciences. 2022;21(3):203-210.

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/909

Chapter 2
Print ISBN: 978-81-976653-0-1, eBook ISBN: 978-81-976653-1-8

Factors Associated with Febrile Treatment-seeking Behaviour among Expectant Mothers in Ssekanyonyi, Mityana District, Uganda

Nanjobe Uniah [a], David R. Mutekanga [a*], Christopher Ddamulira [a], Stephen S. Kizza [b] and Lawlence Sserwanga [a]

DOI: https://doi.org/10.9734/bpi/dhrni/v1/12289F

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/12289F

ABSTRACT

Background: Febrile disease is very common among pregnant women in developing countries and sometimes not given relevant due diligence and perceived as a minor or common malaria situation. However, febrile disease most times is accompanied with some major disease condition which is life threatening to the pregnant women. This is a serious health problem that contributes greatly to morbidity and mortality in most developing economies including Uganda. In Mityana District of Uganda, 4 in 10 pregnancy deaths are malaria related and mothers who do not seek treatment in health facilities when they experience febrile illnesses. This is a major health challenge. Aim: The present study was undertaken to identify factors associated with treatment-seeking behavior among pregnant women suffering from febrile illnesses suspected to be malaria in Ssekanyonyi Sub-County in Mityana District, Uganda.
Methods: A cross-sectional study in which questionnaires were administered to 198 expectant mothers to generate data on their socio-demographics and treatment seeking behaviour. SPSS software version 20.0 was used for data analysis and a Logistic Regression model was fitted to identify factors that independently influenced their treatment-seeking behavior. Relevant REC authorization and standard operating procedures of the Uganda Ministry of Health were duly followed.

[a] Department of Public Health, Bugema University, Kampala, Uganda.
[b] Department of Pathology/ Non-Communicable Diseases, Central Public Health Laboratories, Kampala, Uganda.
**Corresponding author: E-mail: balekemutekanga@gmail.com;*

Results: Out of the198 expectant mothers enrolled in the study, 42.9% were aged 15-25 years, 73.7% had achieved Secondary education, and 46.5% were married. The treatment-seeking behavior was found to be standing at only 56.6%. Among the different factors studied, health education on malaria (AOR = 3.68, P = 0.000), the attitude of midwives (AOR = 1.45, P = 0.003), patient care (AOR = 0.33, P = 0.030), and attitude of the pregnant mother (AOR = 5.38, P = 0.000) were found to be statistically significantly associated with treatment-seeking behavior among pregnant mothers with febrile illnesses. The results show that the attitude of midwives is significantly associated with treatment-seeking behavior for febrile illnesses assumed to be malaria among pregnant mothers.
Conclusion: The study concluded that health education and awareness on malaria, attitude of midwives and pregnant mothers, and how the pregnant mothers are handled are the most important factors in positively affecting treatment seeking behavior among pregnant mothers with febrile illnesses.
Recommendations: Health education on malaria, midwives' attitudes, patient treatment, and pregnant mothers' attitudes must all be addressed in order to prevent febrile infections. The Ministry of Health and other responsible stakeholders must reinforce health education programs for women of reproductive age about the dangers of febrile illnesses during pregnancy. It is also critical to assist midwives in addressing issues related to their attitudes toward pregnant mothers.

Keywords: Febrile illnesses; malaria fever; pregnancy; treatment seeking behavior; Ssekanyonyi; Uganda.

1. INTRODUCTION

Understanding social and cultural factors that influence health care seeking behaviour is critical for ensuring safe pregnancies and deliveries. Women are at further risk of morbidity and mortality due to poor health seeking practices and limited access to health facilities. There is a gross deficiency in the distribution of health facilities [1]. Treatment-seeking behavior for febrile illnesses assumed to be malaria among pregnant women is of greater concern than in other groups at risk [2,3]. Febrile illnesses can lead to abortion, intrauterine fetal death, premature delivery, and even maternal death in case pregnant mothers do not seek treatment in time [4,3,5]. Febrile morbidity can be an intriguing entity in the maternal period. Fever during pregnancy causes significant maternal and fetal complications. Any acute or chronic infectious diseases may be aggravated during the period of pregnancy [6].

Previous studies indicate that factors such as insufficient health education, the attitude of midwives, and myths about sickness during pregnancy are the major hindrances to treatment seeking among pregnant mothers even though they are exposed to febrile illnesses [7,8]. The majority of the mothers depend financially on their husbands for health support, yet the majority of the vulnerable mothers are found in poverty-stricken countries and families where many use herbal medication before seeking conventional treatment [9,10,11,3,8]. They further

reported that health education in rural areas is said to be unconvincing yet mothers are aided to shun health units due to the bad attitude of some midwives during the antenatal visits. Although most mothers in rural areas cover long distances to health centers, there are several other factors that seem to influence treatment-seeking behavior among pregnant mothers when they experience febrile illnesses [8].

Globally 88% of women access antenatal care at least once in pregnancy [10]. This presents an opportunity for pregnant women to access several health care services including treatment of febrile illnesses assumed to be malaria [10] while others seek help from herbalists and drug shops [8]. Available epidemiologic studies of malaria and febrile illnesses in pregnancy (MIP) by Ding et, al., [12] found that many mothers were not seeking treatment due to low income and distance, yet malaria was associated with adverse maternal and neonatal outcomes including maternal anemia, preterm labor, stillbirths, and low birth weight. In developing economies in Africa the situation is not any better [10].

In Africa several authors [10,13] have highlighted the overall burden of febrile illnesses assumed to be malaria among pregnant mothers is high and its adverse outcomes to the pregnant mother and the unborn child are widespread. In countries south of the Sahara in Africa, despite the growing awareness about the pregnancy-associated febrile illness and the need for treatment, research has revealed that community members still attribute malaria to bed bugs and other insects [8]. In Ethiopia for example, more than three-quarters of the landmass (altitude <2000 m) of the country is malaria endemic, and pregnant women and under-five years old children are the most vulnerable groups [14].

In Uganda, malaria manifested in febrile illnesses is a serious health challenge that contributes greatly to morbidity and mortality in this country [15]. The situation in Mityana District, Uganda was grave with 45% of pregnant mothers failing to seek treatment in health facilities when they experience febrile illnesses while 4 in 10 pregnancy deaths are malaria-related [16,8].

The above situation called for a need to identify factors associated with treatment-seeking behavior among pregnant women suffering from febrile illnesses suspected to be malaria in Ssekanyonyi Sub-County in Mityana District, Uganda. The specific objectives were to [8]:

- Identify the treatment seeking behaviour of pregnant mothers,
- Establish the factors associated with treatment seeking behaviour of pregnant mothers, and
- Show the relationship between the factors associated with treatment seeking behaviour and the treatment seeking behaviour itself

2. METHODS

The study adopted descriptive design with a cross sectional approach to collect behavioral reactions from different respondents when they experience febrile illnesses. Only quantitative research approaches were used. The study was

descriptive to allow the researcher to discover patterns in the respondents thinking and also to describe issues from their own point of view [8]. Data was collected during the months of March to June 2023. The quantitative approach was used to analyze primary data from the field using descriptive statistic to describe the state of reactions to febrile illnesses assumed to be malaria in Ssekanyonyi Sub County and discussion in relationship to interview results. The correlations design was used to establish relation between variables [8].

2.1 Setting

The study was conducted in Ssekanyonyi Sub County in Mityana District, Uganda. Ssekanyonyi is located 20 kilometers by road from Mityana Municipality.

2.2 Population and Sample Size

Ssekanyonyi sub county target population was 9,532 identified from 5 health units receiving and registering pregnant women (Table 1 below) [17]. The sample size of 321 was determined using the Krejcie and Morgan [18] formula and relevant proportional numbers from each of the 5 health centers determined using the Kothari [19] allocation sampling formula (Table 1) [8].

Table 1. Target population and sample size

Health Center	Target Population	Sample Size
Ssekanyonyi HC IV	4396	162
St Padre Pio HV III	2066	70
Bussunju HC III	1086	32
Bussunju Police HC II	998	29
Kassikombe HC II	986	28
Total	**9532**	**321**

However, during the data collection, the response rate was only (198) 62%. This was mainly because most of the pregnant mothers were unwilling to respond without authorization from their husbands who unfortunately were not available at the health facility.

2.3 Sampling and Data Collection Instruments

A simple random sampling procedure was employed to select 198 respondents.

Sampling was done by selecting two respondents followed by leaving out the next two respondents till the two total number of days given for data collection from each health center ended.

The study used a questionnaire as tool in data collection. The questionnaire was validated using 10 pregnant mothers who report on different days from those the sample report. Some very minor corrections were done on the questionnaire after validation, then it was used. The questionnaire collected quantitative data from the 198 individuals.

2.4 Data Analysis

Data collected was analysed using the SPSS software version 20.0 and a Logistic Regression model was fitted to identify factors that independently influenced their treatment-seeking behavior.

2.5 Ethical Considerations

Informed consent was obtained from the respondents prior to data collection then the researcher establish rapport and proceeded with the interview in a private quiet room. Anonymity and privacy of the participants was observed. The participants remained anonymous during the whole process of the study [8]. The participants' information was kept confidential and only used for the purpose of this study. Relevant ethical authorization was obtained from the local Research Ethics Committee (REC) of Mulago Hospital and Uganda National Council for Science and Technology (UNCST) as required by law in Uganda. On top of this the relevant standard operating procedures of the Uganda Ministry of Health were duly followed [8].

3. RESULTS

A total of 198 respondents were sampled. The social demographic data was collected and the results are given in Table 2 below [8].

Table 2. Social demographic characteristics of respondents

Item	Frequency (n = 198)	Percent (%)
Age (years)		
15-25	85	42.9
26-35	71	35.9
36-45	42	21.2
Level of education		
Non formal	18	9.1
Primary	34	17.2
Secondary	146	73.7
Marital Status		
Single	12	6.1
Married	92	46.5
Divorced/Separated	10	5.1
Widowed	8	4.0
Cohabiting	76	38.4

From results in Table 2 above, a higher proportion (57.1%) were in the age bracket of 26 to 45 years. The majority (73.7%) were secondary level graduates, and only 46.5% were married.

The results for objective one identifying the treatment seeking behaviour among pregnant women in this sub county are shown in Table 3 [8].

Table 3. Treatment seeking behaviour among pregnant women

Item	Frequency (n = 198)	Percent (%)
Seeking Treatment		
Have you had malaria symptoms when pregnant?		
Yes	120	60.6
No	78	39.4
If yes, did you go for medical treatment immediately you felt feverish?		
Yes	112	(93.3)
No	8	(6.7)
Health care service provider		
Finding health workers at the health center?		
Yes	147	74.2
No	51	25.8
Adherence		
Observing the dosage as prescribed for malaria treatment.		
All the time	(88)	(73.3)
Most of the time	(30)	(25)
Never	(2)	(1.7)

The results from Table 3 above show that majority (60.6%) of the respondents reported having ever had malaria symptoms when pregnant. Of these, 93.3% reported that they went for medical treatment immediately they felt the symptoms [8].

The majority (74.2%) of all the respondents reported that they had never missed or failed to find health workers at the health center when they go for medication. A higher percentage (73.3%) of those who went for malaria treatment reported that all the time they observe the dosage as prescribed by the medical worker for malaria treatment [8].

The results for objective two which was establishing the factors associated with treatment seeking behavior are shown in Table 4 [8].

The results in Table 4 shows that the majority (77.8%) 0f the respondents have never attended or participated in any village seminar or community training on health and / or malaria. The majority (93.9%) of the respondents have never had health workers visiting their homes to talk about malaria issues [8].

However, the majority (86.9%) reported that the midwives have a positive attitude towards the expectant mothers and indeed the majority (86.9%) reported receiving warm welcome from health workers when they visit the health centers [8]. This is further confirmed by the majority (84.8%) reporting that they feel they should be coming back to the health centre whenever they get malaria. Also, most of the respondents (63.6%) reported that the medical workers usually test malaria using a kit. However a slightly above average (56.6%) reported that they had ever been told that the health unit has no malaria medicine [8].

Table 4. Factors associated with treatment seeking behaviour

Items	Frequency (n = 198)	Percent (%)
Health Education on Malaria		
Have you ever attended village seminars on health and / or malaria?		
Yes	44	22.2
No	154	77.8
Have health workers ever visited your home and spoke about malaria issues		
Yes	12	6.1
No	186	93.9
Attitude of midwives		
Do midwives have positive attitude towards expectant mothers?		
Yes	172	86.9
No	26	13.1
Patient Care		
Do you get warm welcome from the health workers?		
Yes	172	86.9
No	26	13.1
Do you feel you should always come back to the heath center whenever you get malaria?		
Yes	168	84.8
No	30	15.2
Medical Supplies and Equipment		
Do medical workers test malaria with a kit?		
Yes	126	63.6
No	72	36.4
Have you been told that there were no malaria medicines in the health center?		
Yes	112	56.6
No	86	43.4
Distance (km) from Home to Health center		
less than 1 km	75	37.9
1-2 km	73	36.9
2-5 km	50	25.3
Income Level		
How much income per month?		
Less than US $13.5	124	62.6
US $13.5 to 27.0	74	37.4
Attitude of the Pregnant Mother		
Does malaria have sdverse effects on pregnancy		
Yes	170	85.9
No	28	14.1

Table 5. Relationship between the factors and treatment seeking behaviour

Variables	Treatment Seeking		UOR (95% CI)	p-value	AOR (95% CI)	p-value
	Sought n (%)	**Not Sought n (%)**				
Health education on Malaria						
Attended training	104 (86.6)	16 (13.4)	**3.46 (2.56 – 3.98)**	**0.000****	**3.68 (2.91 – 4.39)**	**0.000****
Did not attend training	50 (64.1)	28 (35.9)	**1**		**1**	
Attitude of midwives						
Positive	110 (91.7)	10 (8.3)	**2.57 (1.88 – 3.01)**	**0.000****	**1.45 (0.93 – 2.05)**	**0.003****
Negative	74 (94.9)	4 (5.1)	**1**		**1**	
Patient Care						
Good care	115 (95.8)	5 (4.2)	**2.55 (1.75 – 3.23)**	**0.000****	**8.22 (6.45 –10.96)**	**0.030****
Not caring	70 (89.7)	8 (10.3)	1		1	
Medical supplies and equipment						
Have equipment	94 (78.4)	26 (21.6)	2.52 (1.67 – 3.42)	0.000**	0.79 (0.26 – 1.31)	0.650
No equipment	32 (41)	46 (59)	1		1	
Distance						
Short	113 (76.3)	35 (23.6)	0.314 (0.112 – 0.754)	0.052		
Long	36 (72)	14 (28)	1			
Income level						
High	14 (21.8)	50 (78.1)	0.047 (0.013 – 0.101)	0.828		
Low	113 (84.3)	21 (15.6)	1			
Attitude of the pregnant mother						
Positive	100 (83.3)	20 (16.7)	**5.53 (4.87 – 5.97)**	**0.000****	**5.38 (4.87 – 6.17)**	**0.000****
Negative	50 (64.1)	28 (35.9)	**1**		**1**	

**p < 0.05* ***p < 0.01* *RC=1* ***Significant at 5%*

Most of the respondents (76.8%) travel 2 or less kilometers to the health center. This means the health centers are easily accessible.

The majority (62.6%) reported having a monthly income level of less than US dollars 13.5. This very low but understandable because this is rural area and these are women who commonly earn nothing and stay at home mothers v.

However, most of them (85.9%) are aware that malaria has adverse effects on pregnancy.

The third and last objective (3) was to show the relationship between the factors and the treatment seeking behavior of these mothers. The results are show in Table 5.

From Table 5, the analyzed results revealed that health-based factors had a significant association to treatment seeking behaviour among pregnant women suffering from febrile illnesses assumed to be malaria. Health education on malaria, attitude of midwives and patient care had a significant association with treatment seeking behaviour among pregnant women suffering from febrile illnesses assumed to be malaria [8]. The adjusted odds ratio of health education on malaria [AOR = 3.68, (CI 95% = 2.91 – 4.39), p=0.000] implies that the odds of treatment seeking behaviour among pregnant women who had attended training on malaria were about 4 times higher compared to those who did not attend training on malaria. While the adjusted odds ratio of attitude of midwives [AOR = 1.45, (CI 95% = 0.93 – 2.05), p=0.003] implies that the odds of treatment seeking behaviour among pregnant expectant mothers who reported positive attitude of midwives were 1.45 times higher as compared to those who reported negative attitude of midwives [8]. On the other hand, the adjusted odds ratio of patient care [AOR = 8.22, (CI 95% = 6.45 – 10.96), p=0.030] implies that the odds of treatment seeking behaviour among pregnant expectant mothers who they were given good care by the medical workers at the health units were 8 times higher compared to those who were not given good care by the medical workers at the health units [8]. Other health-based factors such as medical supplies and equipment and distance to health unit had no significant association to treatment seeking behaviour among pregnant expectant mothers [8].

Personal factors also had a significant association with treatment seeking behaviour among pregnant expectant mothers. Attitude of pregnant mother was the only personal factor that had a significant association with treatment seeking behaviour among pregnant expectant mothers [8]. The adjusted odds ratio malaria [AOR = 5.38, (CI 95% = 4.87 – 6.17), p=0.000] imply that the odds of treatment seeking behaviour among pregnant expectant mothers who had had positive attitude towards the midwives were about 5 times higher compared to those who had negative attitudes. Other personal factors such as income level had no significant association to treatment seeking behaviour among pregnant

expectant mothers. The quantitative results were consistent with the qualitative results [8].

4. DISCUSSION

The study found that health education on malaria is significantly associated with treatment-seeking behavior for febrile illnesses. This implies that when pregnant mothers are given varied sessions of training to acquire knowledge about malaria, they are more likely to seek treatment immediately after they experience changes in their body temperate [8]. This can contribute to fighting deaths among mothers caused by other febrile illnesses. The findings above are consistent with other researchers [20,21] who reported that the failure to establish the level of knowledge of community members regarding malaria appeared to be responsible for the inability of intervention programs to achieve sustainable control [8]. This is very important for the Ministry of Health which organizes education and awareness programs for the communities.

The results also show that the attitude of midwives is significantly associated with treatment-seeking behavior for febrile illnesses assumed to be malaria among pregnant mothers. This implies that when pregnant mothers are handled well, they will always seek treatment for febrile sicknesses assumed to be malaria. These findings are supported by earlier researchers [22,23,8] who earlier reported that nurses should be good to their patients in order to encourage them to report for medical care should they feel unwell especially pregnant women during antenatal care and labour. It is thought that poor customer handling may be a large contributor towards scaring away mothers even when they get malaria. This is crucial for the Ministry of Health which supervises training colleges of Nurses and Midwives in Uganda.

As observed from the findings, patient care was significantly associated with treatment-seeking behavior among respondents. The findings suggested that the health workers were aware of their obligations to the clients. Other reports [24] noted that it is important that expectant mothers are given relevant patient care that can propel them to always seek hospital treatment whenever they are in need [8]. According to some authors [25], whenever mothers have considerably changed their moods, the health workers should be in position to give comfort and contain their emotions.

Also, the attitude of pregnant mothers was found to be significantly associated with treatment-seeking behavior for pregnant mothers having febrile illnesses assumed to be malaria. This is a major factor in health promotion aspects of the community where health workers should try to be diligent when serving special populations. In support of the above findings several authors [26,27,28,8] reported that expectant mothers are simply negligent about seeking health treatment when they are sick of malaria but they are actually aware of the challenges caused by the delayed treatment of malaria. However, they further reported that it is not certain whether mood swings alone can deter mothers from seeking malaria treatment but what is known is that mother's attitude towards the

treatment of malaria can cause undesirable health challenges if poorly managed [8].

The limitation of this study was the fact that it was cross sectional in nature and data was collected at a single point in time which may not necessarily allow changes in behavior to surface. Qualitative longitudinal studies with in-depth interviews could have provided more insights after passage of time about how the expectant mothers change in treatment-seeking with changes in various situations [8].

5. CONCLUSION

From the study, health education on malaria, the attitude of midwives, patient care, and the attitude of the pregnant mothers were found to be significantly associated with treatment-seeking behaviors among pregnant women suffering from febrile illnesses assumed to be malaria [8]. This calls for a need to intensify awareness programs on health education among women of reproductive age about the danger of febrile illnesses during pregnancy and assist midwives to individually and collectively address issues affecting their attitude towards pregnant mothers [8].

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

ACKNOWLEDGEMENT

The authors wish to appreciate the Department of Public Health School of Graduate Studies Bugema University for the support and facilities provided for the research and write up of this report.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Akeju DO, Oladapo OT, Vidler M, Akinmade AA, Sawchuck D, Qureshi R, Solarin M, Adetoro OO, von Dadelszen P. CLIP Nigeria Feasibility Working Group. Determinants of health care seeking behaviour during pregnancy in Ogun State, Nigeria. Reproductive Health. 2016 Jun;13:67-74.
2. Kigozi BK, Kharod GA, Bukenya H, et al. Investigating the etiology of acute febrile illness: A prospective clinic-based study in Uganda. BMC Infectious Diseases. 2023;23(1):411.
Avaialble:https://doi.org/10.1186/s12879-023-08335-4

3. WHO. World Malaria Report 2023; 2023. Avaialble:www.who.int/teams/global-malaria-programme
4. Mvondo JL, James MA, Cambell CC. Malaria and pregnancy in Cameroonian women. Effect of pregnancy on Plasmodium falciparum parasitaemia and the response to chloroquine. Tropical medicine parasitology. 2012;43(5)1-5.
5. Peeling RWW, Fongwen N. Solving the enigma of acute febrile illness. The Lancet Infectious Diseases. 2022;22(9):1261-1262. Published: June 15, 2022. DOI: https://doi.org/10.1016/S1473-3099(22)00313-9
6. Poovathi M, Prasanna N. Fever in pregnancy and its maternal and fetal outcome at tertiary care level. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2018 May 1;7(5):1864-8.
7. Adedokun ST, Yaya S. Factors influencing mothers' health care seeking behaviour for their children: Evidence from 31 countries in sub-Saharan Africa. BMC Health Serv Res. 2020;20:842. Avaialble:https://doi.org/10.1186/s12913-020-05683-8
8. Uniah N, Ddamulira C, Kizza SS, Sserwanga L, Mutekanga DR. Factors Associated with Febrile Treatment-Seeking Behaviour among Expectant Mothers in Ssekanyonyi, Uganda. International Journal of Tropical Disease & Health. 2023 Dec 2;44(23):1-9.
9. Chepkemoi A, Mutulei N. Factors Influencing the Uptake of Intermittent Preventive Treatment for Malaria in Pregnancy: Evidence from Bungoma East District, Kenya. Science and Education Publishing; 2014. Avaialble:http://pubs.sciepub.com/ajphr/1/5/2/index.html Retrieved on 3rd March 2016.
10. UNICEF. Antenatal care is essential for protecting the health of women and their unborn children; 2024. Avaialble:https://data.unicef.org/topic/maternal-health/antenatal-care/
11. WHO. WHO informal consultation on fever management in peripheral health care settings: A global review of evidence and practice; 2013. ISBN 978 92 4 150648 9.
12. Ding XC, Incardona S, Serra-Casas E, Charnaud SC, Slater HC, Domingo GJ, et al. Malaria in pregnancy (MiP) studies assessing the clinical performance of highly sensitive rapid diagnostic tests (HS-RDT) for Plasmodium falciparum detection. Malaria Journal. 2023;22(1):60. Avaialble:https://doi.org/10.1186/s12936-023-04445-1
13. Wainaina M, Attuy Vey da Silva D, Dohoo I, et al. A systematic review and meta-analysis of the aetiological agents of non-malarial febrile illnesses in Africa. PLOS Neglected Tropical Diseases; 2022. Published: January 24, 2022. Avaialble:https://doi.org/10.1371/journal.pntd.0010144
14. Adugna T, Zelalem L, Alelign G. Blood smears examination and prevalence of malaria in Addis Zemen Town, Northwest Ethiopia (2013-2021): A retrospective study. Tropical diseases, travel medicine and vaccines. 2024;10(1):12. Avaialble:https://doi.org/10.1186/s40794-024-00219-y

15. Nakisuyi J, Bernis M, Ndamira A, Kayini V, Mulumba R, Theophilus P, Agwu E, Lule H. Prevalence and factors associated with malaria, typhoid, and co-infection among febrile children aged six months to twelve years at kampala international university teaching hospital in western Uganda. Heliyon. 2023;9(9):e19588.
Avaialble:https://doi.org/10.1016/j.heliyon.2023.e19588
16. Zalwango MG, Bulage L, et al. Trends and Distribution of severe Malaria cases in Uganda - 2017nto 2021: Analysis of Health Management Information System Data. UNIPH Bulletin Articles. 2023;8(2).
Avaialble:https://uniph.go.ug/trends-and-distribution-of-severe-malaria-cases-uganda-2017-2021-analysis-of-health-management-information-system-data/
17. UBOS. 2021 Uganda Statistical Abstract; 2021.
Avaialble:http://library.health.go.ug/sites/default/files/resources/UBOS%20Statistical%20Abstract%202021.pdf
18. Krejcie R, Morgan DW. Determining Sample Size for Research Activities. Economic Psychological Measurement. 1970;607-610.
19. Kothari CR. Research Methodology - Methods and Techniques (2nd Revised Edition). Published by New Age International (P) Ltd, Publishers; 2004.
20. Munzhedzi M, Rogawski McQuade ET, Guler JL, et al. Community knowledge, attitudes and practices towards malaria in Ha-Lambani, Limpopo Province, South Africa: A cross-sectional household survey. Malar J. 2021;20(188).
Avaialble:https://doi.org/10.1186/s12936-021-03724-z
21. Andegiorgish AK, Goitom S, Mesfun K, Hagos M, Tesfaldet M, Habte E, Azeria E, Zeng L. Community knowledge and practice of malaria prevention in Ghindae, Eritrea, a Cross-sectional study. African health Sciences. 2023;23(1):241–254.
Avaialble:https://doi.org/10.4314/ahs.v23i1.26
22. Maharaj R, Mohammadnezhad M. Perception of Health Care Workers (HCWs) towards early antenatal booking in Fiji: A qualitative study. PloS One. 2022;17(11):e0276805. A
Avaialble:https://d2004oi.org/10.1371/journal.pone.0276805
23. Drigo L, Masane Luvhengo Rachel T Lebese, Lufuno Makhado. Attitudes of Pregnant Women Towards Antenatal Care Services Provided in Primary Health Care Facilities of Mbombela Municipality, Mpumalanga Province, South Africa. The Open Public Health Journal. 2020;13:TOPHJ-13-569.
DOI: 10.2174/1874944502013010569
24. WHO. Maternal Health and Safe Motherhood Programme. Maternity care: What is needed for safer motherhood in the community?. Safe Motherhood. 1992;8:6–8.
Avaialble:https://pubmed.ncbi.nlm.nih.gov/12285230/
25. Modak A, Ronghe V, Gomase KP, Mahakalkar MG, Taksande V. A Comprehensive Review of Motherhood and Mental Health: Postpartum Mood Disorders in Focus. Cureus. 2023;
15(9):e46209. Avaialble:https://doi.org/10.7759/cureus.46209

26. Musoke D, Ndejjo R, Wafula ST, Kasasa S, Nakiyingi-Miiro J, Musoke MB. Malaria health seeking practices for children, and intermittent preventive treatment in pregnancy in Wakiso District, Uganda. African Health Sciences. 2021;21(4):1722–1732.
Avaialble:https://doi.org/10.4314/ahs.v21i4.28
27. Taremwa IM, Ashaba S, Kyarisiima R, et al. Treatment-seeking and uptake of malaria prevention strategies among pregnant women and caregivers of children under-five years during COVID-19 pandemic in rural communities in South West Uganda: A qualitative study. BMC Public Health. 2022;22(373).
Avaialble:https://doi.org/10.1186/s12889-022-12771-3
28. Mpimbaza A, Nayiga S, Ndeezi G, Rosenthal PJ, Karamagi C, Katahoire A. Understanding the context of delays in seeking appropriate care for children with symptoms of severe malaria in Uganda. PLoS ONE. 2019;14(6):e0217262.
Avaialble:https://doi.org/10.1371/journal.pone.0217262

Biography of author(s)

David R. Mutekanga (PhD)
Department of Public Health, Bugema University, Kampala, Uganda.

He is an Associate Professor at Bugema University in Uganda. With a biological sciences background, he holds a Master of Sciences in Applied Entomology and Parasitology and a PhD in Environment Management. His major research in the interdisciplinary areas of environment and public health, environment and natural resources, environment and rural development. He has published over 35 research-based papers more recently on environmental health challenges in developing countries in sub-Saharan Africa in the management of health at the health facilities level.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
International Journal of Tropical Disease & Health, 44(23): 1-9, 2023. DOI: 10.9734/IJTDH/2023/v44i231499

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/12289F

Chapter 3
Print ISBN: 978-81-976653-0-1, eBook ISBN: 978-81-976653-1-8

Reliability of the Fitness Gram test in Assessing Physical Fitness among School Children in Guwahati, North-east India

Pranjal Gogoi [a*] and Nirmal C. Bhattacharyya [b]

DOI: https://doi.org/10.9734/bpi/dhrni/v1/953

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/953

ABSTRACT

Background: The physical fitness is an integrated measure of the body functions involved in the performance of daily physical activity and physical exercise. Childhood and adolescence are crucial periods of life, where physiological and psychological changes take place at these age. Both cardiorespiratory and muscular fitness in children are important for positive health behaviour.
The assessment of physical fitness using a specific tool has become an important part to find out the fitness level of children and adolescence. Fitness gram is a health-related fitness test that utilizes criterion-referenced standards on health-related components. Through the years research has shown that Fitness gram has become one of the most widely used programs in the United States, though its use in India is not popular.This study aims to evaluate the interrater reliability of the Fitness Gram test, a widely used tool for physical fitness assessment, among school children in the urban society of Guwahati, North-East India.
Methods: A sample of 70 school children aged 5-14 years was assessed using the Fitness gram test battery. Students were randomly allocated for physical fitness test where 62 students have completed the test.Two trained raters independently scored the tests. Statistical analysis was done by Cronbach's Alpha value has been computed for the Interrater reliability.
Results: Sixty-two students with both gender (male 56.3% and female 43.7%, age -10.12±2.72) were assessed for physical fitness using Fitness gram test

[a] Department of Physiotherapy, Downtown Hospital ltd, Guwahati, Assam, India.
[b] Department of Pediatric Surgery, Gauhati Medical College, Guwahati, Assam, India.
**Corresponding author: E-mail: pranjal_gogoi25@rediffmail.com;*

battery. All the test variables showed an excellent reliability (Cronbach's alpha =0.91-0.95).
Conclusions: Fitness Gram test demonstrates high interrater reliability for assessing physical fitness in school children in Guwahati. These findings support its use as a reliable tool in school-based fitness assessments, potentially aiding in the development of targeted fitness programs.

Keywords: Fitness gram test; inter-rater reliability; pediatric population; physical fitness.

1. INTRODUCTION

Physical fitness is generally considered to be "the ability to perform daily tasks without fatigue." Definition of physical fitness is given differently by different people. It is defined as the ability to meet life's demand and still have enough energy to respond to unplanned events [1]. Physical fitness includes cardiorespiratory fitness, muscular endurance, muscular strength, flexibility, coordination, and speed. Evidence-based research indicates that physical fitness is a powerful marker of health in children and adolescents [2]. In particular, cardiorespiratory endurance [3] and muscle strength [4] have been found to be positively associated with markers of health in children and adolescents. It has been seen that a high level of physical fitness in childhood and adolescence is related to better health-related outcomes, which are concerned with present and future risk for obesity, cardiovascular disease, skeletal health and mental health [2]. In a study done in South Africa where the author has done physical fitness test among school children from both rural and urban area and found a high prevalence of low fitness among children from the urban school aged 12 years (63.9%), 6 years (63.2%), and 11 years (60%) in contrast to the the prevalence of low fitness among rural based learners aged 12, 6, and 11 years equalled 18.9%, 39.3%, and 20% respectively.The finding suggests that sedentary lifestyle in urban population may cluster around the period that a child approaches the adolescent stage of life as adolescents are more likely to spend much time with social media devices [5]. As such the assessment of physical fitness using a specific tool has become an important part to find out the fitness level of children and adolescence. There were several fitness test batteries for the assessment of physical fitness in children and their reliability and validity has been established by different author in accordance to different geographical area. The appropriate fitness test that promoted exercise and fitness was still under examination [6]. In response to this, a study concluded that any fitness test which promotes enjoyment and motivation to do physical activity should be accepted and encouraged [7]. Such a fitness test is Fitness gram. Through the years research has shown that Fitness gram has become one of the most widely used programs in the United States, though its use in India is not popular [8].

Fitness gram is a health-related fitness test that utilizes criterion-referenced standards on health-related components. Fitness gram includes a variety of health- related physical fitness tests designed to assess cardiovascular fitness, muscle strength, muscular endurance, flexibility, and body composition [9]. These

standards are age and gender specific and are established based on how fit children need to be for good health. Fitness gram was developed in 1982 by The Cooper Institute in response to the need in physical education for a detail and comprehensive assessment, and with the vision of helping enhance the effectiveness of school- based physical education [10,11]. In accordance to the present health and reduced risk of disease, the Fitness gram standards were developed and the results were the minimal levels of fitness which is consistent [12].

This study aims to evaluate the interrater reliability of the FitnessGram test, a tool for physical fitness assessment, among school children in the urban area of Guwahati, North-East India with present and future risk for obesity, cardiovascular disease, skeletal health and mental health [2]. As such the assessment of physical fitness using a specific tool has become an important part to find ou the fitness level of children and adolescence.

2. METHODS

A small exploratory study was conducted with a prior consent from the parents of school children to assess the inter-rater reliability of Fitness gram test in a school of Guwahati urban society, a capital city of northeastern India. Age between 5 to 14 years of school children,70 subjects were included in the study by using random sampling method with both the genders randomly selected and allocated for the screening. All grades covering 5 to 14 years with either gender participated in the Fitness gram® assessment test for physical fitness (Cooper Institute for Aerobics Research, 1999). The students having a history of medical, neurological, orthopedic (including wore any type of orthotic device), balance or visual disorders, any acute illness, recent trauma or fall and those children with difficulty in understanding about the test procedure were excluded from the study.

Eight participants were excluded from this analysis leaving a final sample of 62 participants. In order to participate in the study written consent were taken from the parents. Appropriate ethical clearance taken from Institutional ethical committee of Gauhati Medical College, Guwahati, Assam. Two physiotherapists as a rater were allotted for Interrater reliability test and the children were screen by the two raters with Fitness gram test batteries in a gap of one week. The first rater conducts the fitness test among the selected students and the same subjects were again assessed by the second rater after 1 week [9]. The two raters were blinded from each other findings. The subjects were included randomly irrespective of any musculoskeletal pain, pyrexia, and any inflammatory joint disease, clumsy child as referred by parents or any neurological problems. If any red flags found in the subjects, then immediate referral to a hospital or a concern medical setup was made.

Using Fitness gram for assessing the physical fitness of school children. The selected students were assessed with Fitnessgram test battery. The physiotherapist followed the procedures outlined in the Fitness gram® manual

updated fourth edition to provide feedback on correct form [6]. Each test of Fitness gram was demonstrated to the students prior to their participation and corrective test position has been maintained for each selected student. The tests were conducted in a group of 6 children at a time to avoid any chaos and confusion. The detail procedure of the test battery was given in (Table 1).

Table 1. Procedure of the fitness gram test battery

Aerobic capacity (Pacer)	**Student was instructed to run as long as possible with continuous movement back and forth across a 20-meter space at a specified pace that gets faster with each minute.**	
Body composition	Skin fold measurement	The triceps skin fold is measured on the back of the right arm over the triceps muscle, midway between the elbow and the acromion process of the scapula. The calf skinfold is measured on the inside of the right leg at the level of maximal calf girth. The right foot is placed flat on an elevated surface with the knee flexed at a 90^0 angle.
	Body mass index	BMI = weight (kg) / height $(m)^2$
Abdominal strength and endurance (Curl up)	The student is made to lie in supine position on the mat, knees bent at an angle of approximately 140^0, feet flat on the floor, legs slightly apart, arms straight and parallel to the trunk with palms of hands resting on the mat. A measuring strip is placed on the mat so that fingertips are just resting on the nearest edge of the measuring tape. Keeping heels in contact with the mat, the student curls up slowly; sliding fingers across the measuring strip until fingertip reach the other side. Movement should be slow, and the student continues without pausing until he or she no longer continue or has completed 75 curl ups.	
Trunk extensor strength and flexibility (Trunk lift)	The student being tested lies on the mat in a prone position with hands placed under the thighs. Maintaining the head in a neutral alignment with the spine the student lifts the upper body off the floor, in a very slow and controlled manner, to a maximum height of 12-inches. The distance from the floor to the student's chin is determined.	
Upper body strength and endurance (90^0 Push up)	The student being tested assumes a prone position on the mat with hands placed under or slightly wider than the shoulders, fingers stretched out, legs straight and slightly apart, and toes tucked under. The student pushes up off the mat with the arms until arms are straight, keeping the legs and back straight.	
Flexibility (Shoulder stretch)	The students need to touch the fingertips together behind the back by reaching over the shoulder and under the elbow. To test the right shoulder student reaches with the right hand over the right shoulder and down the back as if to pull up a zipper or scratch between the shoulder blades. At the same time places the left hand behind the back and reaches up, trying to touch the fingers of the right hand.	

2.1 Statistical Analysis

Data were pooled and put under statistical analysis. The two observer's score were lined up in the excel sheet where the qualitative data of shoulder reach test was coded into quantitative data. Each component of the Fitness gram test battery was analyzed for inter rater reliability. Interrater reliability was done with independent ratings of the same event with two raters. No discussion or collaboration occurred when reliability is tested. Reliability is determined by the correlation of the scores from two independent raters (for ratings on a continuum).

Cronbach's Alpha value has been computed for the Interrater reliability. The mean and standard deviation for the age, height and weight were computed. Each component of Fitnessgram test battery were analysed for range, mean and standard deviation and was compared between both the raters. Statistical Package for Social Survey (SPSS) for Windows, version 20 and Microsoft excel was used to find out the reliability coefficient.

3. RESULTS

3.1 Demographic Information

There were 70 students involved in the study. However, 62 students had complete data with no missing values, thus, the response rate was 88.57%. The sample population were both males and females constituting male with 56.3% and female with 43.7%. Demographic details including age, height and weight were described in (Table 2). The overall students mean age was 10.12±2.72 years. The mean height of the whole study participants was 140.9±17.1 cm. The overall mean weight of the students was 36.8±12.5 kg. The BMI (Body mass index) mean for the whole study population was 18.46±3.43 (Table 2).

Overall, raters demonstrated acceptable to excellent agreement on each of variable in Fitness gram for the total sample. The two assessor's mean and SD for different variables of Fitness gram has minimal difference. An excellent reliability has been found when two raters assessed the individual variables i.e. $\alpha \geq 0.9$. As shown in the (Table 3). The VO_2 max calculated by both the raters on the same students were in the range of 32.2 mL/kg/min to 43.9 mL/kg/min where the difference between minimum values is 0.5 and the maximum values is also 0.5. The overall mean of the VO_2 max as measured by rater 1 and rater 2 were 38.157±2.28 and 38.24±2.25 respectively (Table 3). The curl up repetitions were measured and the minimum and maximum values has some differences where some students showed increase in repetition on second attempt with the second rater though the mean and standard deviation doesn't have significant difference. The mean number of curl ups as measured by rater 1 and rater 2 were 17.1667±7.15 and 17.8636±7.31 (Table 3). The number of repetitions of push up doesn't have differences between the first attempt and the second attempt. The range of 0 to 30 numbers of pushups by the students with mean value

4.86±5.88 and 5.63±6.08 during first and second attempt as measured by rater 1 and rater 2 respectively has shown an excellent inter-rater reliability of the test (Table 3). The trunk lifts by the students in the both instances have similar raise (in inches) of the trunk above the ground with excellent inter-rater reliability (≥0.9) of the test. The mean inches raise of the ground was 8.8182±2.74 inch and 9.7576±2.73 inch as measured by rater 1 and rater 2 respectively (Table 3).

The shoulder reach test has result in qualitative form and was quantified into numerical 0 and 1. The contact of the student's fingertip of both the hand at the back has been coded 0 and the one which doesn't have been coded 1. The inter-rater reliability was found to be acceptable (0.73). The body composition measured with skin fold measurement and Body Mass Index were having similar scores measured by both the raters and Cronbach's alpha value of 0.99 found. The overall mean of skin fold measurement was 12.51±6.50 mm and 12.57±6.46 mm as measured by rater 1 and rater 2 respectively (Table 3).

Table 2. Demographic details of the participating school children

	Mean (62)	**SD**
Age	10.12	2.72
Height	140.9	17.1
Weight	36.8	12.5
BMI	18.46	3.43

Table 3. Inter rater reliability of different components of Fitness gram test

N=62		**Min-max**	**Mean±SD**	**Cronba ch's alpha**
	Rater 1	32.3-43.4	38.157±2.28	
Pacer	Rater 2	31.7-43.9	38.24±2.25	0.959
Skin	Rater 1	4-35	12.51±6.50	
Fold	Rater 2	4-35	12.57±6.46	0.99
	Rater 1	5-32	17.166±7.15	
Curl up	Rater 2	2-39	17.863±7.31	0.949
	Rater 1	0-27	4.8636±5.88	
Push up	Rater 2	0-30	5.6364±6.08	0.941
Trunk	Rater 1	3-12	8.8182±2.74	
Lift	Rater 2	4-11	9.7576±2.73	0.914
Shoulder	Rater 1	0-1	0.8939±0.31	
Reach	Rater 2	0-1	0.9091±0.28	0.73

4. DISCUSSION

This small exploratory study investigates the inter-rater reliability of Fitness gram test battery to be used for assessing the physical fitness of children with reference to the pediatric population of Guwahati, a capital city of northeast India. This is the first study to report the reliability of a physical fitness test. The components of Fitness gram test battery consist of different variables where each of the variables counts its own importance and the general physical fitness of a

children depends not only on one variable instead has to consider all the components of Fitness gram. Hence, when physical fitness is tested, the functional status of all these systems is actually being checked. This is the reason why physical fitness is nowadays considered one of the most important health markers, as well as a predictor of morbidity and mortality for cardiovascular disease (CVD) and for all causes [13-18]. The measurement of aerobic capacity through PACER where number of laps measuring 20 meters were covered by the students in two different instances and was found to be similar. The actual VO_2 max and VO_2 max measured by PACER laps does not have significant difference [9]. Measuring aerobic fitness using the criterion measure VO_2 max requires expensive equipment and is thus not feasible for administration in a school or many clinical settings. Instead, several field tests are commonly used [10]. One of the studies provide an excellent example of determining the criterion-referenced reliability of the Fitness gram's PACER and 1-mile walk/run items [7]. The assessment is evaluated using criterion-referenced standards that reflect the amount of fitness needed for good health. In the study the aerobic capacity VO_2 max was compared with the Criterion-referenced standards. A quadratic equation was used to find the VO_2 max where gender of the child, BMI and number of laps were used [9]. The quadratic equation used for calculating aerobic capacity is, VO_2 max = 41.77+0.49 (laps) - 0.0029 (laps) 2 - 0.62(BMI) + 0.35 (gender × age), Where gender, 0 for girls, 1 for boys was used. Criterion- referenced standards are more useful for fitness evaluation since it makes it possible for individuals to compare their overall fitness to an absolute criterion (The Cooper Institute, 2011). From age 5 years to 9 years the number of laps were not recommended to find out the aerobic capacity though the Fitness gram recommended for participation in the run. These standards help to place the individual in either the Health Fitness Zone (HFZ) or the Needs Improvement Zone (NI). In this study the results of VO_2 max by both the rater were within the range as provided in the criterion referenced standards for healthy fitness zone. The curl up, trunk lift and push up were done to assess the strength and endurance of muscles. They all showed an excellent reliability. This may be due to the reason that muscle physiology of the individual doesn't get change until any injury or pathological changes takes place. The reliability coefficient of shoulder stretch test was found to be 0.73 which is acceptable but the reason for this variation from other components may be due to some minimal error from the part of the assessor and the students. The body composition measured by means of skin fold measurement and Body mass index were found to be similar as measured by both the raters and this absolute similar result was found as there was no loss of weight in the said duration and nor has chance of reduction of height. Skin fold variation is less likely to change in this short duration of gap. There is strong evidence indicating that cardiorespiratory fitness levels are associated with total and abdominal adiposity, when adiposity is assessed either by anthropometric indexes or by reference methods such as Dual Energy X-ray Absorptiometry, computed tomography or magnetic resonance imaging [19].

In the fitness testing, most of the tests involve maximum effort that results in lasting fatigue (e.g., PACER Test, mile run/walk, 900 push-up test, curl-up test) and due to this the student's maximum aerobic capacity, strength and endurance

can be easily determined [8]. The scores of Fitness gram test can be influenced by some of the factors and to make the scores meaningful the tester need to fulfil certain condition like maintaining privacy more in the case of body composition measurement and also the scores can be influenced by making the fitness test as an integral part of teaching and providing health related concepts [8]. The scores result of this study can be compared with the criterion referenced standard scores to evaluate the relationship between them using an appropriate statistical test.

Additional research on establishment of normative data of physical fitness of pediatric population in India is needed by using Fitness gram test battery.

5. CONCLUSION

Study has enlightened the requirement of Fitness gram test for assessing the physical fitness of the pediatric population in Guwahati urban society which has excellent intra-rater reliability. Based upon this study Fitnessgram test can be used in other parts of the country or as a whole to established a geographical based criterion reference scores in order to determine the association of fitness and other health outcomes, evaluate the effectiveness of training programs designed to increase fitness, and determine the prevalence of adequate levels of fitness. In school settings, Fitness gram tests can be implemented for other purposes, to provide individualized feedback to students about their fitness levels and make recommendations for increasing or maintaining current fitness levels.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that no generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee of Gauhati Medical College, Guwahati, Assam, India.

ACKNOWLEDGEMENTS

Authors would like to thank the principal and the entire faculty member of Shankardev shishu niketan, Maligaon, Guwahati, Assam, India for their support and their arrangement. Also would like to thank Prof.(Dr) Kabul Chandra Saikia , Retired Principal, Gauhati Medical College for his guidance and support.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985 Mar;100(2):126-31.
2. Ortega FB, Ruiz JR, Castillo MJ, Sjöström M. Physical fitness in childhood and adolescence: a powerful marker of health. Int J Obes. 2008;32:1–11.
3. Mintjens S, Menting MD, Daams JG, van Poppel MNM, Roseboom TJ, Gemke RJBJ. Cardiorespiratory fitness in childhood and adolescence affects future cardiovascular risk factors: A systematic review of longitudinal studies. Sports Med. 2018;48:2577–605. Available:https://doi.org/10.1007/s40279-018-0974-5
4. García-Hermoso A, Ramírez-Campillo R, Izquierdo M. Is muscular fitness associated with future health benefits in children and adolescents? A systematic review and meta-analysis of longitudinal studies. Sports Med. 2019;49:1079-94. Available:https://doi.org/10.1007/s40279-019-01098-6.
5. Olagbegi O M, Nadasan T, Mazibuko Y, Mfenga E, Rangana K, Themba R. Physical fitness profile of rural versus urban primary school children in eThekwini district, KwaZulu-Natal, South Africa. Human Movement. 2022;23(3):140-9. Available:https://doi.org/10.5114/hm.2022.107974
6. Fox KR, Biddle SJ. The use of fitness tests: Educational and psychological considerations. J Physic Edu, Recrea Dance. 1988 Feb 1;59(2):47-53.
7. Ernst MP, Corbin CB, Beighle A, Pangrazi RP. Appropriate and inappropriate uses of FITNESSGRAM®: A commentary. J Phys Act Health. 2006 Jan 1;3(s2):S90-100.
8. Meredith MD, Welk GJ. In: Fitnessgram and activitygram Test Administration Manual. Dallas, TX: Cooper Institute Aerobics Res. 2010:9-10.
9. Rubín, Lukáš, Suchomel, Aleš. Test batteries assessing physical fitness in school-aged children in the Czech Republic: A brief review. Scientific Review of Physical Culture. 2013;3:96–102.
10. Mahar MT, Guerieri AM, Hanna MS, Kemble CD. Estimation of aerobic fitness from 20-m multistage shuttle run test performance. Am J Prevent Med. 2011 Oct 1;41(4):S117-23.
11. Morrow JR, Falls JR HB, Kohl HW. In: The Prudential Fitnessgram technical reference manual. 4th edition. III. (Eds.). Dallas; TX: Cooper Institute Aerobics Research. 1994;7-8.
12. Mahar MT, Rowe DA. Practical guidelines for valid and reliable youth fitness testing. Measure Physic Edu Exercise Sci. 2008 Jul 29;12(3):126-45.
13. Boiarskaia EA, Boscolo MS, Zhu W, Mahar MT. Cross-validation of an equating method linking aerobic FITNESSGRAM® field tests. Am J Prevent Med. 2011 Oct 1;41(4):S124-30.
14. Safrit MJ, Baumgartner TA, Jackson AS, Stamm CL. Issues in setting motor performance standards. Quest. 1980 Jul 1;32(2):152-62.

15. Beets MW, Pitetti KH. Criterion-referenced reliability and equivalency between the PACER and 1-mile run/walk for high school students. J Phys Act Health. 2006 Jan 1;3(s2):S21-33.
16. Blair SN, Kohl III HW, Paffenbarger Jr RS, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA 1989; 262: 2395–2401.
17. Mora S, Redberg RF, Cui Y, Whiteman MK, Flaws JA, Sharrett AR et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: A 20-year follow-up of the lipid research clinics prevalence study. JAMA. 2003;290:1600–1607.
18. Metter EJ, Talbot LA, Schrager M, Conwit R. Skeletal muscle strength as a predictor of all-cause mortality in healthy men. J Gerontol A Biol Sci Med Sci 2002; 57: B359–B365
19. Ortega, Francisco, Ruiz Jonatan, Castillo Manuel, Sjostrom Michael. Physical fitness in childhood and adolescence: A powerful marker of health. International Journal of Obesity. 2008;2005(32):1-11. DOI: 10.1038/sj.ijo.0803774

Biography of author(s)

Dr. Pranjal Gogoi (Ph. D)
Department of Physiotherapy, Downtown Hospital ltd, Guwahati, Assam, India.

Research and Academic Experience: He is working as an Associate Professor and has 14 years of research and academic experience.

Research Specialization: He is specialized in orthopedic physiotherapy, physical fitness, pediatric health and fitness.

Number of Published papers: He has published 8 national and international articles in reputed journals.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
International Journal of Research in Medical Sciences, 8(1): 312-316, 2020.
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20195928

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/953

Chapter 4
Print ISBN: 978-81-976653-0-1, eBook ISBN: 978-81-976653-1-8

Flow Cytometry Indicators in Mycosis Fungoides/Sezary Syndrome: Unveiling Silent Disease

C. C. Kariyawasan [a*], B. L. T. Balasuriya [a] and S. A. C. D. Ranatunga [a]

DOI: https://doi.org/10.9734/bpi/dhrni/v1/983

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/983

ABSTRACT

Mycosis Fungoides (MF) is the most common type of cutaneous T-cell lymphoma, accounting for 50% of all cutaneous lymphomas. Sezary Syndrome (SS) and MF are closely related T-cell neoplasms that are considered separately based on clinical features and cell of origin. Despite their differences, both conditions can be challenging to diagnose, particularly in the absence of clinical symptoms. Flow cytometry plays a crucial role in the diagnosis of MF and SS, with a characteristic immunophenotypic expression that includes the lack of CD7 as a common feature in all stages of the disease. This diagnostic tool is invaluable in identifying the specific markers that differentiate these lymphomas from other T-cell disorders. In clinical practice, it is not uncommon to encounter patients who are asymptomatic yet exhibit a flow cytometric profile indicative of MF/SS. Such cases are rarely documented in the literature, highlighting the need for increased awareness and detailed analysis of these silent presentations. Persistent lymphocytosis, for example, can be an initial finding that warrants further investigation through flow cytometry. The immunophenotypic profile of MF/SS typically includes bright positivity for markers such as smCD3, CD4, CD2, TCRαβ, and CD5, with dim positivity for CD8. Conversely, markers such as CD7, TCRγδ, CD25, and CD26 are usually negative. The CD4+/CD8+ ratio is often altered, reflecting the underlying pathophysiology of these lymphomas. Despite the absence of clinical symptoms, such as those required by the International Society of Cutaneous Lymphomas (ISCL) and the European Organization for Research and Treatment of Cancer (EORTC) for staging MF and SS, the presence of a typical immunophenotypic pattern on flow cytometry is significant. It underscores the importance of utilizing advanced diagnostic techniques to uncover and manage

[a] *Sri Jayewardenepura General Hospital, Thalapathpitiya Nugegoda, Sri Lanka.*
**Corresponding author: E-mail: chitrak64@yahoo.com;*

silent diseases effectively. By understanding the flow cytometry indicators and their implications in the context of MF/SS, clinicians can better identify and treat patients who might otherwise remain undiagnosed until the disease progresses to more advanced stages. This knowledge is critical for early intervention and improved patient outcomes in cutaneous T-cell lymphomas.

Keywords: Mycosis fungoides; Sezary syndrome; flowcytometry; skin lesions; ICSL and EORTC staging.

1. INTRODUCTION

Mycosis fungoides (MF) is the most common type of cutaneous T – cell lymphomas, accounting for for 50% of all cutaneous lymphomas [1]. Its reported frequency is heterogeneous worldwide, with an incidence of ~ 0.58 cases per 100,000 person-years in the United States and 0.2–0.37 cases per 100,000 person-years across Europe; however, its incidence is thought to be greatly underestimated [2,3,4,5,6]. They manifest heterogeneous clinical, histologic, immunophenotypic, and cytogenetic features. MF is associated with several professions which have high risk of exposing petrochemical, textile and metal industry, painting, woodworking, and carpentry [1].

Sezary syndrome (SS) and MF are closely related T-cell neoplasms, that are are considered separately on the basis of differences in the clinical features and cell of origin [7]. Despite their differences, both conditions can be challenging to diagnose, particularly in the absence of clinical symptoms. Erythroderma, generalized lymphadenopathy, the presence of clonal neoplastic T cells with cerebriform nuclei (Sezary cells) in peripheral blood, skin and lymph nodes are the main features of the Sezary syndrome. Mycosis fungoides has an indolent course with slow progression over years characterized by patches, plaques and eventually tumours. Both SS and MF patients are adult/elderly and have male predominance [1,7].

Flowcytometry plays an important role in diagnosis of MF and SS with a characteristic immunophenotypic pattern. This diagnostic tool is invaluable in identifying the specific markers that differentiate these lymphomas from other T-cell disorders. In clinical practice, it is not uncommon to encounter patients who are asymptomatic yet exhibit a flow cytometric profile indicative of MF/SS. Such cases are rarely documented in the literature, highlighting the need for increased awareness and detailed analysis of these silent presentations. Persistent lymphocytosis, for example, can be an initial finding that warrants further investigation through flow cytometry. Flowcytometry analysis of peripheral blood lymphocytes of MF shows CD2+, smCD3+, CD4+, TCRαβ+, CD5+, TCRγδ- expression. A lack of CD7 is common in all stages of the disease [8].

The neoplastic T cells of SS have an immunophenotypic pattern of CD3+, CD4+, CD8. Characteristically lack of CD7 and CD26 is common in SS [1]. The CD4+/CD8+ ratio is often altered, reflecting the underlying pathophysiology of these lymphomas. Despite the absence of clinical symptoms, such as those

required by the International Society of Cutaneous Lymphomas (ISCL) and the European Organization for Research and Treatment of Cancer (EORTC) for staging MF and SS, the presence of a typical immunophenotypic pattern on flow cytometry is significant. It underscores the importance of utilizing advanced diagnostic techniques to uncover and manage silent diseases effectively. By understanding the flow cytometry indicators and their implications in the context of MF/SS, clinicians can better identify and treat patients who might otherwise remain undiagnosed until the disease progresses to more advanced stages. This knowledge is critical for early intervention and improved patient outcomes in cutaneous T-cell lymphomas.

Our study is a case of a clinically asymptomatic patient presenting with a flowcytometric pattern of Mycosis fungoides/Sezary syndrome. There was no documentation of such a case in the literature survey.

2. FLOW CYTOMETRIC INDICATORS

A 55 - year – old male presented to a tertiary care hospital on account of persistent lymphocytosis.

There was no history of lymphadenopathy, organomegaly or significant skin lesions. He gave a history of an itchy rash that was previously diagnosed and treated as dermatitis. He did not give a history of radiation exposure but had a childhood history of close contact with *batik dyes*. Investigations revealed a Hb of 15.5 g/dl, ESR 03 mm/1st hour, platelet count – 178,000/cu mm, WBC of 10,700/cu mm and absolute count of lymphocyte of 7000/cu mm (62%). Serum Protein electrophoresis was normal [7]. LDH level was 149 IU/L (150-250) IU/L. And the Chest X-ray showed no acute pathology.

The patient was clinically observed for a period of five months. Investigations carried out in the Haematology clinic included full blood counts (FBC), monospot test, ultrasound scan of abdomen, full body CT scan, LDH level and viral studies. During this period, lymphocytosis persisted with eosinophilia. The counts were as follows, 6332/cu mm, 4918/cu mm, 5749/cu mm, 6890/cu mm and 7820/cu mm. Viral studies revealed CMV IgG antibody positivity and Hepatitis A (HAV) IgG positivity. Studies for HIV were negative. Monospot test was negative. Ultrasound scan of abdomen and full body CT scan were normal. Blood picture revealed small to medium sized lymphocytes with scanty cytoplasm. Bone marrow aspiration biopsy showed reactive marrow with high, normal lymphocyte count [7]. Lymphocyte count was approximately 15 -20% of the nucleated marrow cells. Plasma cells not increased and the blast percentage was less than 3%. The findings of Bone marrow trephine biopsy were consistent with the bone marrow aspiration findings.

To confirm/ exclude chronic lymphoproliferative disorder, flowcytometry was performed using peripheral blood and bone marrow samples.

Flowcytometry of peripheral blood revealed that T-lymphocyte percentage was 92.0%. Accordingly, B- lymphocytes and NON-T/B- cells were 6.0% and 2.0%.

The immunophenotypic results of LST (Lymphoid Screening Tube) and TCLPD (T Cell Lymphoproliferative Disorder) panels showed bright positivity of smCD3, CD4, CD2, TCRαβ, CD5 and dim positive CD8. Negative results were CD7, TCRγδ, CD25, CD26 and CD4+/ CD8+ ratio was 3.0.

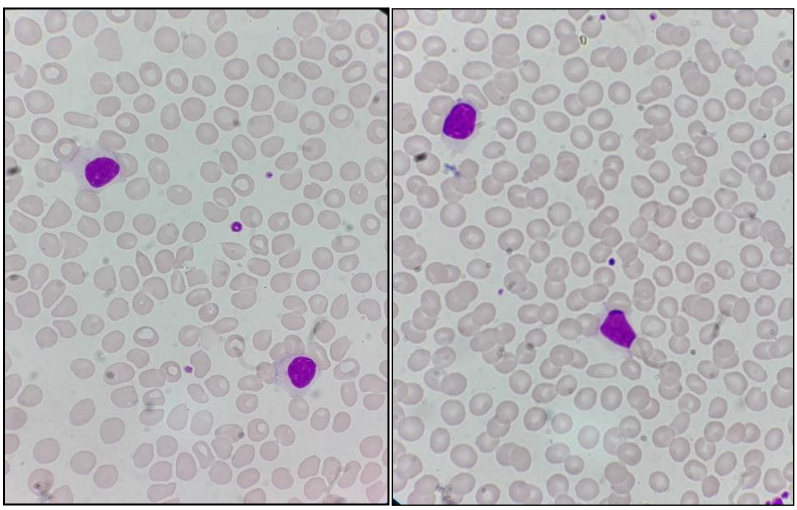


Fig. 1. Morphology of peripheral blood

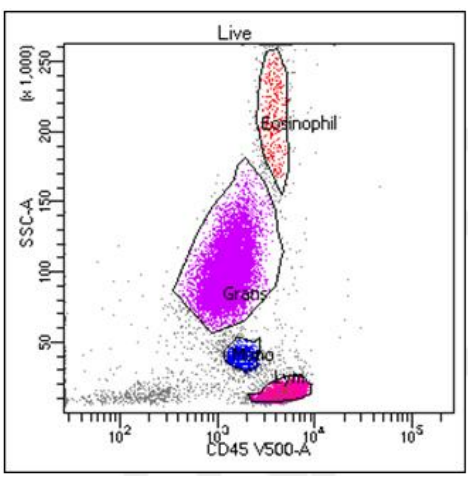


Fig. 2. Live cells gated by CD45

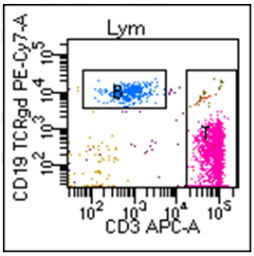


Fig. 3. lymphocytes gated by CD3 and CD19

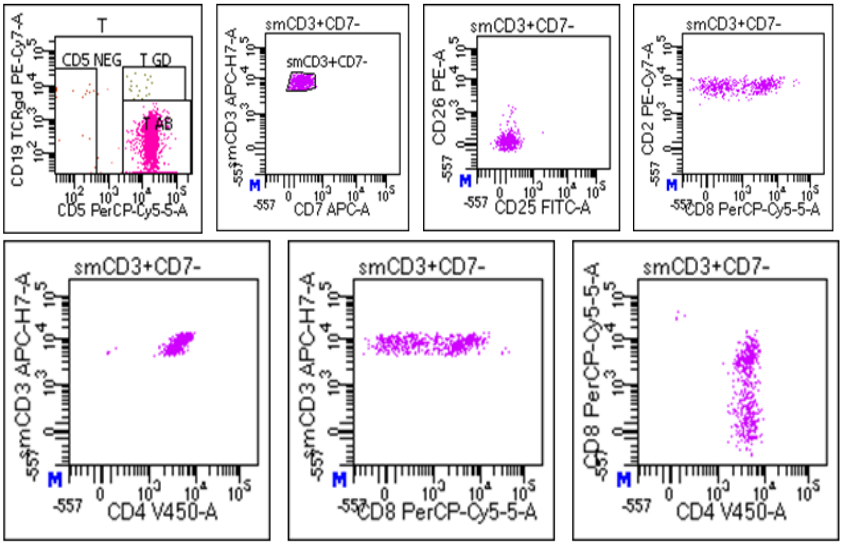


Fig. 4. Flow charts of smCD3 positive, CD7 negative lymphocytes

Flowcytometry of bone marrow revealed that T- lymphocytes percentage was 82.0%. Accordingly, B- lymphocytes and NON-T/B -cells were 16.0% and 2.0%.

The immunophenotypic results of LST and TCLPD panels showed bright positivity of smCD3, CD4, CD2, TCRαβ, CD5 and dim positive CD8. Negative results were CD7, TCRγδ, CD25, CD26 and CD4+/ CD8+ ratio was 2:3 [7].

3. CLINICAL INSIGHTS OF MYCOSIS FUNGOIDES

According to staging of MF/SS by International Society of Cutaneous Lymphomas (ISCL) and the European Organization for Research and Treatment of Cancer (EORTC) criteria, to describe a patient under the stage I(A) (T1,N0,M0,B0-1), he should have at least limited patches, papules and/or plaques covering <10% of the

skin [9]. A patch means a skin lesion of any size without significant elevation or induration [9]. Our patient showed no skin lesions, no abnormal lymph nodes or visceral organ involvement and absence of significant morphological changes of the lymphoid cells in the blood [7].

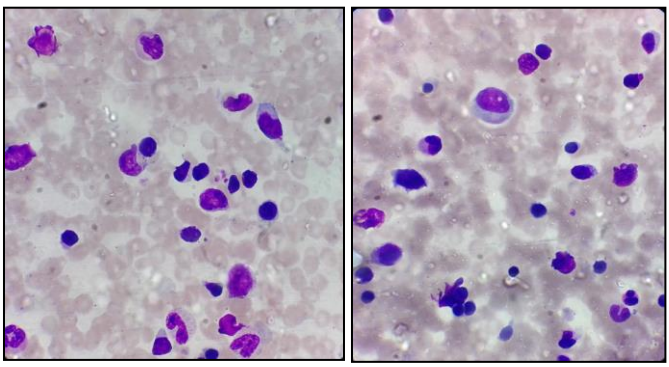


Fig. 5. Morphology of bone marrow

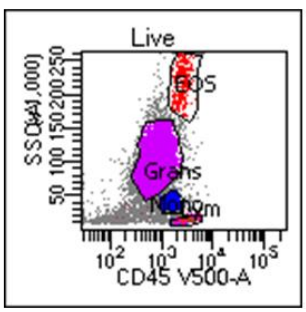


Fig. 6. Live cells gated by CD45

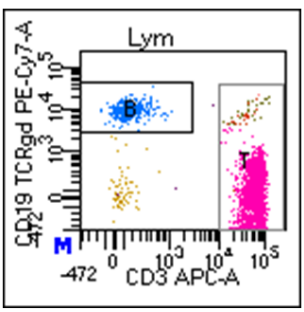


Fig. 7. lymphocytes gated by CD3 and CD19

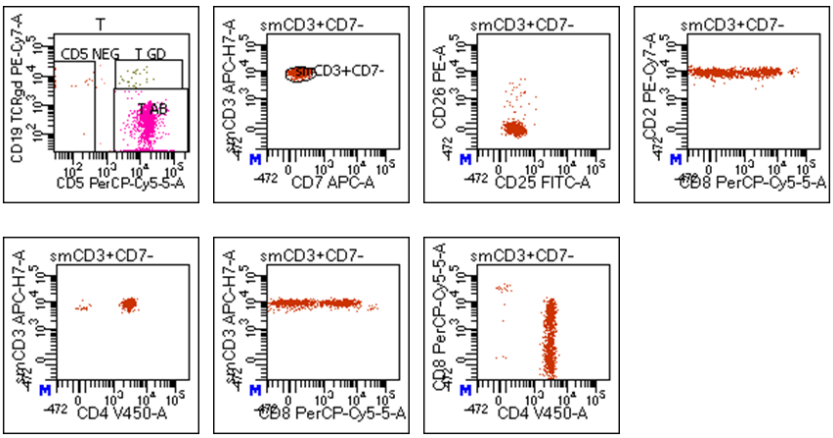


Fig. 8. Flow charts of smCD3 positive and CD7 negative lymphocytes

Premycotic, mycotic, and tumor stage are the three traditional stages of the MF [10]. The blood picture findings of the premycotic stage of the disease are not diagnostic and it is represented by chronic nonspecific dermatitis [11]. As the symptoms and skin biopsy findings are similar to those of other skin conditions it is difficult to diagnose MF in its early stages [12].

Wojdylo MS, et al. [13] showed that flowcytometry analysis of peripheral blood revealed an increased proportion of CD4/CD8 ratio of 8:1 and elevated LDH level (626 U/L). But in our study it was 3/2.3 respectively in blood and bone marrow and LDH was normal.

The neoplastic cells in MF have a pattern of CD3+, CD4+, CD45+ T-cell phenotype with usual expression of TCRαβ+ [7]. Among the pan-T antigens (CD2, CD3, CD5, CD7), CD7 is the most frequently lost antigen. In rare cases of MF, a CD4 – /CD8 + mature T-cell phenotype may be seen [14,15].

In the blood, some of CD4+ T-cells express CD26, whereas neoplastic T-cells in SS display dim CD26 and often aberrant expression of CD7 [16,17].
The clonality of Sezary Syndrome can be proved at the molecular level. The most frequent genetic lesions include monosomy 10, losses of 10q and 17p, gains of 8q24 and 17q, and diverse structural alterations involve in these regions [7,18].

In Mycosis fungoides, most common imbalances are gain of chromosome regions 1p36,7, 9q34, 17q24-qter, 19, and loss of 2q36-qter, 9p21 and 17p [19].

4. FUTURE DIRECTIONS

The criteria of International Society of Cutaneous Lymphomas (ISCL) and the European Organization for Research and Treatment of Cancer (EORTC) to stage

Mycosis fungoides and Sezary Syndrome were not present in our patient who was asymptomatic but showed a typical immunophenotypic pattern of MF/SS [7]. A case report by Laboto B A D L et al. [20] illustrates the challenges in diagnosing early-stage MF. It emphasizes delays in diagnosis can lead to worsened prognosis and potential treatment complications.

While most cases of MF typically exhibit an elevated CD4 to CD8 ratio, a study by Fatima S el al., [21] revealed that this ratio is not consistently increased in all 60 cases they analyzed. Instead, it may be decreased or unchanged, adding another layer of complexity to the immunophenotypic diagnosis. Another case study recently revealed that a case of invisible and asymptomatic mycosis fungoides, confirmed with immunohistochemically and T-cell receptor gene rearrangement studies [22]. This study highlights the importance of alert examination of all tissue specimens for evidence of unrelated pathologic findings.

5. CONCLUSION

The immunophenotypic profile of MF/SS typically includes bright positivity for markers such as smCD3, CD4, CD2, TCRαβ, and CD5, with dim positivity for CD8. Conversely, markers such as CD7, TCRγδ, CD25, and CD26 are usually negative. The CD4+/CD8+ ratio is often altered, reflecting the underlying pathophysiology of these lymphomas. Despite the absence of clinical symptoms, such as those required by the International Society of Cutaneous Lymphomas (ISCL) and the European Organization for Research and Treatment of Cancer (EORTC) for staging MF and SS, the presence of a typical immunophenotypic pattern on flow cytometry is significant. It underscores the importance of utilizing advanced diagnostic techniques to uncover and manage silent diseases effectively. By understanding the flow cytometry indicators and their implications in the context of MF/SS, clinicians can better identify and treat patients who might otherwise remain undiagnosed until the disease progresses to more advanced stages. This knowledge is critical for early intervention and improved patient outcomes in cutaneous T-cell lymphomas.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

Written informed consent was obtained from the patient for publication of this case report.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. 4 Ed. 2017;385-391.
2. Dobos G, Pohrt A, Ram-Wolff C, Lebbé C, Bouaziz JD, Battistella M, et al. Epidemiology of cutaneous T-cell lymphomas: a systematic review and meta-analysis of 16,953 patients. Cancers (Basel). 2020;12(10):2921.
DOI: 10.3390/cancers12102921. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
3. 3. Kaufman AE, Patel K, Goyal K, O'Leary D, Rubin N, Pearson D, et al. Mycosis fungoides: developments in incidence, treatment and survival. J Eur Acad Dermatol Venereol. 2020;34(10):2288–2294.
DOI: 10.1111/jdv.16325. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
4. 4. Maguire A, Puelles J, Raboisson P, Chavda R, Gabriel S, Thornton S. Early-stage mycosis fungoides: Epidemiology and prognosis. Acta Derm Venereol. 2020;100(1):adv00013.
DOI: 10.2340/00015555-3367. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
5. 5. Ottevanger R, de Bruin DT, Willemze R, Jansen PM, Bekkenk MW, de Haas ERM, et al. Incidence of mycosis fungoides and Sezary syndrome in the Netherlands between 2000 and 2020. Br J Dermatol. 2021;185(2):434–435.
DOI: 10.1111/bjd.20048. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
6. Hodak E, Geskin L, Guenova E, Ortiz-Romero PL, Willemze R, Zheng J, Cowan R, Foss F, Mangas C, Querfeld C. Real-Life barriers to diagnosis of early mycosis fungoides: An international expert panel discussion. American journal of Clinical Dermatology. 2023 Jan;24(1):5-14.
7. Kariyawasan CC, Balasuriya BL, Ranatunga SA. A Clinically Asymptomatic Patient with a Flowcytometry Profile of Mycosis Fungoides/Sezary Syndrome.
8. Gorczyca W. Flowcytometry in neoplastic hematology morphologic–immune-phenotypic correlation. 2nd Ed. 2010;230-234.
9. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: A proposal of the International Society for Cutaneous Lymphoma (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007;110(6):1713-1722.
10. Murphy GF, Schwarting R. Cutaneous lymphomas and leukemias. In Lever's histopathology of the skin. Lippincot Williams and Wilkins. 9th Ed. 2005;927–978.

11. Khunger JM, Khunger N, Azad K, Srivastava S. Mycosis fungoides: A case report. Indian Journal of Hematology and Blood Transfusion. 2008;26(1):12–14.
12. Akinbami AA, Osikomaiya BI, John-Olabode SO. Mycosis fungoides: Case report and literature review. Clinical Medicine Insights: Case Reports. 2014;7:95–98.
13. Wojdyło MS, Rybak WB, Cegielska A. Atopic dermatitis-like Pre-Sézary Syndrome: Role of immunosuppression. Acta Dermato-Venereologica. 2011;91: 574–577.
14. Berti E, Tomasini D, Vermeer MH, et al. Primary cutaneous CD8-positive epidermotropic cytotoxic T cell lymphomas. A distinct clinicopathological entity with an aggressive clinical behavior. American Journal of Pathology. 1999;155:483–92.
15. Whittam LR, Calonje E, Orchard G, et al. CD8-positive juvenile onset mycosis fungoides: An immunohistochemical and genotypic analysis of six cases. Br J Dermatol. 2000;143:1199–204.
16. Foucar K. Mature T-cell leukemias including T-prolymphocytic leukemia, adult T-cell leukemia/lymphoma, and Sezary syndrome. American Journal of Pathology. 2007;127:496–510.
17. Jones D, Dang NH, Duvic M, et al. Absence of CD26 expression is a useful marker for diagnosis of T-cell lymphoma in peripheral blood. American Journal of Clinical Pathology. 2001;115:885–92.
18. Izykowska K, Przybylski GK. Genetic alterations in Sezary Syndrome. Journal Leukaemia and Lymphoma. 2011;52(5): 745-753.
19. Prochazkova M, Chevret E, Mainhaguiet G, et al. Common chromosomal abnormalities in mycosis fungoides transformation. Genes, Chromosomes and Cancers. 2007;46(9):828-838.
20. Laboto B A D L, Brito J A G D S M D Carneiro T X et al, Late diagnosis of mycosis fungoides: a case report: Rev Amaz Saude:2021:12:1-5.
21. Fatima S, Siddiqui S, Tarig M U et al, Mycosis Fungoides: A Clinicopathological Study of 60 Cases from a Tertiary Care Center,Indian Journal of Dermatology. 2020:;65(2):123–129.
22. Peters D O K; Onajin M D O, Luzuriaga R et al, An Asymptomatic Case of Invisible Mycosis Fungoides, The American Journal of Dermatopathology. 2023:45(6): 409-410.

Biography of author(s)

Dr. (Ms). C. C. Kariyawasan (MBBS, Diploma in Pathology, MD in Haematology)
Sri Jayewardenepura General Hospital, Thalapathpitiya Nugegoda, Sri Lanka.

She was born in 1964 in Colombo, Sri Lanka. She received undergraduate medical training at the North Colombo Medical College, Sri Lanka, and obtained 2nd class honours at the final MBBS. Her postgraduate qualifications include a Diploma in Pathology and an MD in haematology from the Post Graduate Institute of Medicine (PGIM), University of Colombo, Sri Lanka in the year 2002 and 2004 respectively.

Currently, she is a Consultant Haematologist at the Sri Jayewardenepura General Hospital (SJGH) and Post Graduate Training Institute. She has held this post since 2009. Prior to joining SJGH, she was a senior lecturer in Pathology at the Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka for 12 years. She was president of the Sri Lanka College of Haematologists in the year 2015 and a resource person at the Highlights of the American Society of Haematology (ASH) in Asia held in Brisbane in 2016, on the topic of thrombosis.

She has publications in refereed journals on the topics of Multiple Myeloma, Hypereosinophilic syndrome, Immune thrombocytopenic purpura, diabetes mellitus, advanced FBC parameters such as immature platelet fraction and rare findings on flow cytometry analysis. She is currently an examiner for the Diploma and MD in Clinical Haematology examinations conducted by the PGIM. She is a life member of the Sri Lanka College of Haematologists, College of Pathologists of Sri Lanka and the Sri Lanka Medical Association (SLMA). Her other interests include music and theatre having performed in more than 35 stage productions, and 10 television productions and for the first time in 2018, presented publicly her own set of plays written and directed by her.

B. L. T. Balasuriya (B.Sc in Medical Laboratory Sciences (Special), M.Phil. (Haematology-reading)
Sri Jayewardenepura General Hospital, Thalapathpitiya Nugegoda, Sri Lanka.

He was born in Ragama, Sri Lanka on 22nd May 1986. He completed his B.Sc (Special) degree in Medical Laboratory Sciences with 2nd class upper division at the Faculty of Medical Sciences, University of Sri Jayewardenepura in 2012.

He started his career as a Demonstrator at the Department of Allied Health Sciences at the University of Sri Jayewardenepura. Later, He was appointed as a lecturer attached to the Biomedical Science Degree program of the Colombo branch of Management and Science University (MSU), Malaysia. Currently, he is a Medical Laboratory Technologist attached to the Department of Haematology of the Sri Jayewardenepura General Hospital, Sri Lanka since 2016.

He has publications in refereed journals on the topics of Anemia, Multiple myeloma, Hairy Cell Leukaemia, aberrant expression of Acute myeloid leukaemias, Sezary syndrome, and diabetes mellitus. He is a registered Medical Laboratory Technologist of the Sri Lanka Medical Council (SLMC) and the Ceylon Medical College Council (CMCC). He is a member of the College of Medical Laboratory Scientists, Sri Lanka.

S. A. C. D. Ranatunga (B.Sc in Medical Laboratory Sciences (Special), M.Sc in Molecular Pathology)
Sri Jayewardenepura General Hospital, Thalapathpitiya Nugegoda, Sri Lanka.

He was born in Colombo, Sri Lanka on 29th November 1990. He completed his B.Sc. (Special) in Medical Laboratory Sciences at the Faculty of Medical Sciences, University of Sri Jayewardenepura in 2016 and a Certificate course in Practical skills of Molecular Biology and Genetics at the Institute of Research and Development. He has completed his M.Sc. in Molecular Pathology at the Faculty of Medicine, University of Colombo.

He is a Medical Laboratory Technologist at the Department of Haematology of the Sri Jayewardenepura General Hospital, Sri Lanka since 2017. He has published several articles in refereed journals on subfertility of males, Multiple myeloma, Hairy Cell Leukaemia, aberrant expression of Acute myeloid leukaemias and Sezary syndrome.

He is a registered Medical Laboratory Technologist of the Sri Lanka Medical Council (SLMC) and the Ceylon Medical College Council (CMCC). He is a member of the College of Medical Laboratory Scientists, Sri Lanka.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Asian Hematology Research Journal, 3(1): 17-23, 2020. Available: https://journalahrj.com/index.php/AHRJ/article/view/33

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/983

Chapter 5
Print ISBN: 978-81-976653-0-1, eBook ISBN: 978-81-976653-1-8

Aberrant CD Expression in Acute Myeloid Leukaemia- A Cohort Study in Sri Lanka

C. C. Kariyawasan [a*], B. L. T. Balasuriya [a] and S. A. C. D. Ranatunga [a]

DOI: https://doi.org/10.9734/bpi/dhrni/v1/984

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/984

ABSTRACT

Background: Acute leukaemia is defined as the presence of over 20% of blasts cells in the blood or bone marrow. Acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) are the 2 main types. Acute myeloid leukaemia is a cancer of the myeloid lineage of blood cells and it is the commonest form of acute leukaemia in adults with a median age of 65 years. AMLs have characteristic morphological findings and molecular features with different surface and cytoplasmic cluster of differentiation (CD) markers. These CD markers are determined by immunophenotyping/flow cytometry on leukocytes which helps with accurate diagnosis and reproducibility of AMLs. Flow cytometry plays an important role in the diagnosis, sub classification and monitoring of patients with AML. AML generally shows aberrant CD expression or co- expression in relation to normal myeloid cells.
Objective of the Study: Objective of the Study was to evaluate the frequency and the pattern of aberrant CD expression in AML patients referred to a tertiary care hospital in Sri Lanka in comparison to other published data. There was no comparative data available in respect of Sri Lanka.
Materials and Methods: A retrospective descriptive study including 26 cases of AML diagnosed over a period of 12 months were analyzed. Diagnosis of AML was made by morphology of peripheral blood, bone marrow, trephine biopsies, Sudan Black B stain and the immunophenotypic analysis by multiparameter flow cytometry on bone marrow aspirates or peripheral blood. The markers used in flow cytometry were CD 45, CD34, CD19, CD7, smCD3, cyCD3, cyMPO, cyCD79a, CD20, CD15, CD10, CD5, HLADR, CD64, CD13, CD117, CD33, and CD14. The identification of blasts cells was performed using forward scatter (FSC) versus side scatter (SSC) parameters and CD45 intensity versus SSC dot plots.

[a] *Department of Hematology, Sri Jayewardenepura General Hospital, Sri Lanka.*
**Corresponding author: E-mail: chitrak64@yahoo.com;*

Results: Diagnosed AMLs were morphologically classified according to the French-American-British (FAB) Classification (FAB Subtypes). Among the 26 AML patients, 15 cases (57.69%) had the conventional CD antigen expressions of myeloid lineage. Other 11 cases (42.3%) were AML with aberrant expression of CD markers. Aberrancies of cyCD3 and CD7 were observed in 54.5% and 45.4% AML cases, respectively. smCD3 in 1 case out of 11 aberrant AML cases. Co expression of T lymphoid markers with myeloid markers occurred in 23% cases in our study. CD13 was not expressed in 1 case out of 5 AML- M4 cases and 1 case out of 7 AML- M1. CD33 was not expressed in 1 case out of 2 AML -M0 cases.
Conclusion: We conclude that aberrant expression of CD markers is seen in a significant population of AMLs. cyCD 3, CD7 and smCD 3 were the aberrant markers present in our study population with cyCD3 showing highest frequency.

Keywords: Leukocytes; flow cytometry findings; aberrant expression; acute myeloid Leukaemia.

1. INTRODUCTION

Acute leukaemia is defined as the presence of over 20% of blasts cells in the blood or bone marrow at diagnosis. Acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) are the 2 main types of acute leukaemias [1].

AML is a malignant clonal disorder, characterized by myeloid blast proliferation and expansion and block in differentiation, occurring in the setting of ineffective normal hematopoiesis, and resulting in life-threatening cytopenias and transfusion dependency [2,3]. AML is a cancer of the myeloid lineage of blood cells and it is the commonest form of acute leukaemia in adults with a median age of 65 years. It is diagnosed in (10-15)% of the acute leukaemia in childhood [1].

Flow cytometry is a technology that provides rapid multi-parametric analysis of single cells in solution [3,4], which plays an important role in the diagnosis, sub classification (Table 1) and monitoring of patients with AML based on the morphological findings [5-7]. Currently AMLs are classified according to the WHO classification which is based on cytogenetics.

Table 1. French-American-British (FAB) classification of acute myeloid leukaemia

FAB subtype	
AML-M0	AML with minimal differentiated
AML-M1	AML without maturation
AML-M2	AML with maturation
AML-M3	Acute promyelocytic leukaemia
AML-M4	Acute myelomonocytic leukaemia
AML-M5	Acute monoblastic leukaemia
AML-M6	Acute erythroid leukaemia
AML-M7	Acute megakaryoblastic leukaemia

Acute myeloid leukemia generally shows aberrant CD expression or co-expression in relation to normal myeloid cells [5,6]. Several immunophenotypes of blasts cells from AML cases do not show the features of normal CD expression but

exhibit the expression of non –lineage specific CD markers [7]. Aberrant expression of CD markers occurs when blasts abnormally display antigen not typically for their lineage (Myeloid, B- lymphoid, T -lymphoid) and do not meet WHO criteria for mixed phenotype acute leukaemia (MPAL) [8]. Detection of aberrant CD markers by flow cytometry has been applied toward monitoring of residual disease [9].

2. MATERIALS AND METHODS

2.1 Objective of the Study

The study was done to evaluate the frequency and the pattern of aberrant CD expression in acute myeloid leukemia patients referred to a tertiary care hospital in Sri Lanka in comparison to other published data. No data available in respect of Sri Lanka. AML on therapy, MDS associated AML and those transforming from myeloproliferative disorders were excluded. Those AMLs in which certain markers were not applied were also excluded [7].

This retrospective descriptive study includes 26 cases of AML diagnosed over a period of 12 months from January 2019 to December 2019 [7].

Diagnosis of acute myeloid leukaemia was done on the basis of morphology of leukaemic cells in the bone marrow, trephine biopsies, peripheral blood smears, results of Sudan Black B stain and the immunophenotypic analysis by multiparameter flow cytometry for bone marrow aspirates or peripheral blood.

The markers used in the immunophenotypic analysis are the as follows: CD 45, CD34, CD19, CD7, smCD3, cyCD3, cyMPO, cyCD79a, CD20, CD15, CD10, CD5, HLADR, CD64, CD13, CD117, CD33, CD14 [7].

Peripheral blood or bone marrow aspirate was collected in to EDTA anticoagulated tubes. BD FACS Canto TM II Flowcytometer was used and was configured with three lasers to detect up to eight colors. The fluorochromes used were V450, V500c, FITC, PE, PERCP CY5.5, PE CY7, APC, APC H7. The computer workstation was equipped with the calibrated machine with quality control. BD FACS Diva software was used to analyze the results.

The identification of blasts cells was performed using forward scatter (FSC) versus side scatter (SSC) parameters and CD45 intensity versus SSC dot plots. The fluorescence intensities of the blasts were compared with the negative cell population for expression of different CD markers. Expression of a CD marker by more than 20% of the gated population was considered positive [7,10].

3. RESULTS

Diagnosed AMLs were morphologically classified according to the French-American-British (FAB) Classification (FAB Subtypes) and it is shown in the Table 2 [11,7].

Although the median age for AML in adult is documented as 65 years, our study found that it to be 69.5 years, with an age range of 1- to 93 years. No association with aberrant expression was detected based on age or gender.

Among the 26 acute myeloid leukaemia patients, only 15 cases (57.2%) had the conventional CD antigen expressions of myeloid lineage – specific markers. Other 11 cases (42.3%) were AML with aberrant expression of CD markers [7].

cyCD3 showed aberrancy in (54.5%) of aberrant AML cases, CD7 in (45.4%), smCD3 in (9.0%), Co expression of B lymphoid markers with myeloid markers occurred in 0% in our study.

Co expression of T lymphoid markers (CD7, smCD3) with myeloid markers occurred in 23.0% cases in our study. CD13 was not expressed in 1 case out of 5 AML- M4 cases and 1 case out of 7 AML- M1. CD33 was not expressed in 1 case out of 2 AML -M0 cases [7].

4. DISCUSSION

AML is a clonal proliferation of immature hematopoietic precursors involving primarily in the bone marrow. and blood. Immunopheno-typing by flow cytometry plays an important role in diagnosis and classification of AML.

Side scatter (SSC) and immunophenotyping of blasts helps to differentiate subtypes of AMLs. Aberrant expression of CD markers is important finding in acute myeloid leukaemia which represents a poor prognosis [8].

There are many studies that have found aberrant lymphoid CD expression in acute myeloid leukaemia. In our study there were 11 cases (42.3%) with such aberrant expression. There are studies with 48%, 58% and 30% reported by Khalidi et al. and John et al., Azad AK et al. and Zhu et al. respectively [12,6,7].

Table 2. Number of different AMLs

FAB subtypes	Frequency	Percent	Valid percent	Cumulative percent
AML-M0	2	7.7	7.7	7.7
AML-M1	7	26.9	26.9	34.6
AML-M2	4	15.4	15.4	50.0
AML-M3	7	26.9	26.9	76.9
AML-M4	5	19.2	19.2	96.2
AML-M5	1	3.8	3.8	100.0
Total	26	100.0	100.0	

CD 7 is the commonest aberrant marker found in AML in most studies. In our study the frequency was 45.4% (5 out of the 11 cases). A study by Zheng J et al. revealed that the CD 7 expression was 20.5% [13] with 37% and 24% [14,15] in studies of Bahia DM et al and Reading CL et al respectively. Kita K et al. revealed that young

AML male patients with CD 7 expression had a higher incidence of hepatomegaly and central nervous system involvement in contrast to CD7 negative AML patients [16]. It has also been learnt that patients with aberrant expression of CD 7 had responded poorly to the standard chemotherapy with an unfavorable outcome [17].

The aberrant positivity of cyCD3 was the most prominent, 6 out of 11 (54.5%) in our study. Literature survey showed a single study done by Azad A K et al in which the cyCD3 was 8.3% [6,7].

According to the latest revision (2017) by WHO, T cell component of mixed-phenotype acute leukaemia (MPAL) is characterized by a strong expression of cyCD3, usually with the absence of smCD3 [18] and cyCD3 must be expressed strongly to be considered a T cell specific marker. In our study there was dim expression of cyCD3 in all cases (<25%).

Aberrant expression of B lymphoid markers such as CD 19, cyCD79a and CD20 were negative in our study. But studies have revealed CD 19 and CD 20 in ranges of 10% to 25% of AML cases [19,13]. The study done by Khalidi HS et al. showed CD 20 as the most commonly expressed lymphoid antigen [7,12].

Our study shares common ground with other studies listed in the table in its focus on CD7 but also highlights the unique markers (cyCD3, smCD3) not commonly reported in the other studies listed in the table. The different might reflect regional biological variations in AML. The common investigation of CD7 across diverse studies underscores its potential significance in AML diagnosis and prognosis worldwide.

Table 3. Age and gender distribution of population (Years)

Mean Age	62.88
Median Age	69.5
Minimum Age	1
Maximum Age	93
Female	13
Male	13

Table 4. Distribution of acute myeloid leukaemia with aberrant expression

FAB subtypes	Frequency	Percent	Valid percent	Cumulative percent
AML-M0	1	9.1	9.1	9.1
AML-M1	5	45.5	45.5	54.5
AML-M2	1	9.1	9.1	63.6
AML-M4	4	36.4	36.4	100.0
Total	11	100.0	100.0	

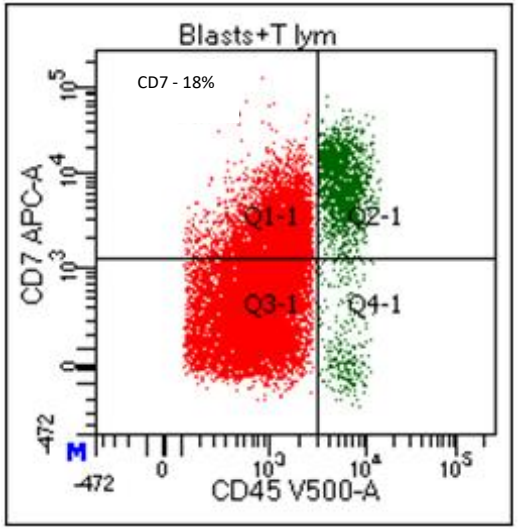


Fig. 1. Aberrant expression of CD7 (32.1%) in blasts (red) in AML- M4

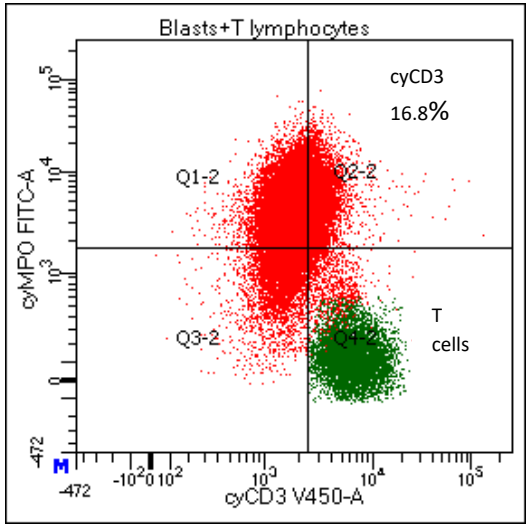


Fig. 2. Aberrant expression of cy CD3 (23.8%) in blasts (red) in AML- M1

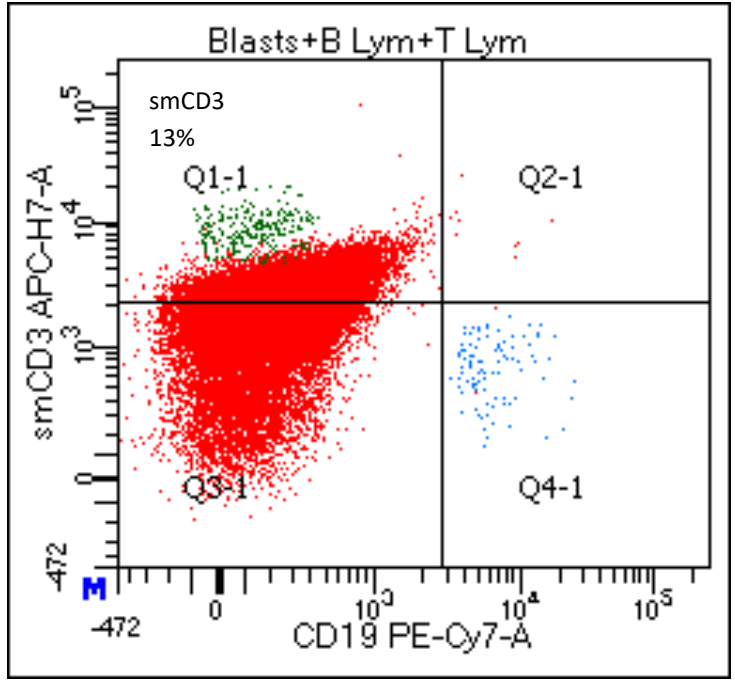


Fig. 3. Aberrant expression of smCD3 (34.1%) in blasts (red) in AML- M2

Table 5. Individual aberrant markers expression in different AMLs

FAB subtypes	Markers expressed								Pan myeloid markers not expressed	
	cyCD3	cyCD79a	CD19	CD7	smCD3	CD20	CD10	CD5	CD13	CD33
AML-M0	1	-	-	-	-	-	-	-	-	1
AML-M1	2	-	-	3	-	-	-	-	1	-
AML-M2	1	-	-	-	1	-	-	-	-	-
AML-M3	-	-	-	-	-	-	-	-	-	-
AML-M4	2	-	-	2	-	-	-	-	1	-
AML-M5	-	-	-	-	-	-	-	-	-	-
AML-M6	-	-	-	-	-	-	-	-	-	-
AML-M7	-	-	-	-	-	-	-	-	-	-
Total	6	0	0	5	1	0	0	0	2	1

Table 6. Distribution of acute myeloid leukaemia with conventional expression

FAB subtypes	Frequency	Percent	Valid percent	Cumulative percent
AML-M0	1	6.7	6.7	6.7
AML-M1	2	13.3	13.3	20.0
AML-M2	3	20.0	20.0	40.0
AML-M3	7	46.7	46.7	86.7
AML-M4	1	6.7	6.7	93.3
AML-M5	1	6.7	6.7	100.0
Total	15	100.0	100.0	

Table 7. Individual conventional markers expression in different AMLs

FAB subtypes	Markers expressed								
	cyMPO	**CD34**	**CD15**	**HLA-DR**	**CD64**	**CD13**	**CD117**	**CD33**	**CD14**
AML-M0	-	2	-	2	-	2	2	1	-
AML-M1	3	6	-	4	-	6	6	7	-
AML-M2	4	3	4	4	1	4	4	4	-
AML-M3	7	1	1	-	-	7	7	7	-
AML-M4	5	2	5	4	4	4	3	5	3
AML-M5	-	-	1	1	1	1	-	1	1
AML-M6	-	-	-	-	-	-	-	-	-
AML-M7	-	-	-	-	-	-	-	-	-
Total	19	14	11	15	6	24	22	25	4

Number	Aberrant Marker	Article	Location	Aim of the study
1	CD7, CD56, CD19	Chen et al. [20]	Taiwan	Retrospective study to characterize the frequency and significance of aberrant antigen expression of AML in Taiwan
2	CD7	Rausei-Mills et al [21]	USA	Analyze the clinical and pathologic features of 15 cases of de novo AML with normal cytogenetics and with FLT3/ITD mutation
3	CD2, CD3, CD7, CD19	Jahedi et al. [22]	Iran	Evaluate the incidence of aberrant phenotypes and possible prognostic value in peripheral blood and bone marrow mononuclear cells of Iranian patients with AML.
4	CD7, CD19	Bahia et al. [23]	Brazil	Analyze 35 cases of AML, examining them for aberrant phenotypes by multiparametric flow cytometry.

Number	Aberrant Marker	Article	Location	Aim of the study
5	CD15, CD56	Breccia et al. [24]	Italy	Assess the frequency of CD15 and CD56 expression, and their prognostic value in a large series of APL patients, uniformly diagnosed and treated according to the AIDA schedule
6	CD56, CD19	Iriyama et al. [25]	Japan	Investigation of the clinical significance for the prognosis of surface antigen expression in patients with AML t(8; 21)
7	CD56, CD7	Abdulateef et al. [26]	Saudi Arabia	Determine the prevalence of aberrant antigen expression in acute leukemia, to assess clinical relevance, and to demonstrate immunophenotype-karyotypic correlations
8	CD7, CD56	Cui et al. [27]	USA	Changes in leukemia-associated aberrant immunophenotype (LAIP) in patient with refractory and relapsed acute myeloid leukemia (AML)
9	cyCD 3, CD7, smCD 3	Kariyawasan C C et al	Sri Lanka	Aberrant CD Expression in Acute Myeloid Leukaemia-A cohort study in Sri Lanka

5. CONCLUSION

We conclude that aberrant expression of CD markers is seen in a significant population of AMLs. cyCD 3, CD7 and smCD 3 were the aberrant markers present in our study population [7]. M0, M1, M2 & M4 AML are associated with aberrant expression. Of these cyCD3 was the commonest.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

As per international standard written patient consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Hoffbrand AV, Moss PAH. Hoffbrand's essential haematology, John Wiley & Sons Ltd. 2010;06:178.
2. DiNardo CD, Erba HP, Freeman SD, Wei AH. Acute myeloid leukaemia. The Lancet. 2023 Jun 17;401(10393):2073-86.
3. Touré SA, Keita M, Seck M, Diallo AB, Gueye SM, Traoré M, Koba C, I D, Motassi E, Dieng F, Faye BF, Sall A, Diop S. Biphenotypic Acute Leukemia: Description of a Case and Literature Review. Int. J. Res. Rep. Hematol. [Internet]. 2023 Feb. 3 [cited 2024 Jun. 8];6(1):38-43. Available:https://journalijr2h.com/index.php/IJR2H/article/view/104
4. McKinnon KM. Flow cytometry: an overview. Current protocols in immunology. 2018 Jan;120(1):5-1.
5. Azad AK, Khan MR, Habib ABMH, Begum M. Uncommon CD markers in acute myeloid leukaemia, Bangabandhu Sheikh Mujib Medical University Journal. 2018;11: 267-269.
6. Azad AK, Khan MR, Habib ABMH, Wadud MA, Begum M. Aberrent expression of CD markers in Acute Myeloid Leukaemia, Haematology Journal of Bangladesh. 2018;2(1):14-16.

7. Kariyawasan CC, Balasuriya BL, Ranatunga SA. Flow Cytometry Findings of Aberrant Expression in a Cohort of Patients with Acute Myeloid Leukaemia. Asian Hematology Research Journal. 2019: 2(4): 138- 143.
8. Hajra S, Panduragan S, Manivannan P, Kar R, Basu D. Aberrant antigenic expression in acute leukemia: Studyfrom a tertiary care center in Southern India, Journal of Hematology and Allied Sciences. 2022 :2(1):10-15.
9. Buccisano F, Maurillo L, Del Principe MI, Del Poeta G, Sconocchia G, Lo-Coco F, Arcese W, Amadori S, Venditti A. Prognostic and therapeutic implications of minimal residual disease detection in acute myeloid leukemia. Blood. 2012;119: 332- 41.
10. Jha R, Grover G, Bose P, Lymphoid associated antigen expression in new cases of Acute Myeloid Leukaemia, Journal of Pathology of Nepal. 2013;3: 487-490.
11. Gorczyca W, Flow cytometry in neoplastic hematology morphologic–immune-pheno-typic correlation. 2nd ed. 2010;136-197.
12. Khalidi HS, Medeiros LJ, Chang KL, Brynes RK, Slovak ML, Arber DA. The immunophenotype of adult acute myeloid leukemia: high frequency of lymphoid antigen expression and comparison of immunophenotype. French-American-British classification and karyotypic abnormalities. American Journal of Clinical Pathology. 1998;109:211–20.
13. Zheng J, Wang X, Hu Y, et al. A correlation study of immunophenotypic, cytogenetic, and clinical features of 180 AML patients in China. Cytometry B Clinical Cytometry. 2008;74:25-9.
14. Bahia DM, Yamamoto M, Chauffaille Mde L et al. Aberrant phenotypes in acute myeloid leukemia: A highf requency and its clinical significance. Haematologica. 2001; 86:801-6.
15. Reading CL, Estey EH, Huh YO, et al. Expression of unusual immunophenotype combinations in acute myelogenous leukemia. Blood. 1993;81:3083–90.
16. Kita K, Miwa H, Nakase K, et al. Clinical importance of CD7 expression in acute myelocytic leukemia. The Japan Cooperative Group of Leukemia/ Lymphoma. Blood. 1993;81:2399- 405.
17. Rai S, Singh S, Gupta R, Prognostic significance of CD56 and CD7 in acute myeloid leukaemia and their outcome, American Journal of Blood Research. 2020;10(4):109-117.
18. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4ed. 2017;179-181.
19. Khurram MM, Jafri SA, Mannan A, Nadeem A, Jamal A. Frequency of aberrant expression of CD markers in cases of acute leukemia. Medical Journal of Islamic World Academy of Science. 2010;18:55-60.
20. Chen SW, Li CF, Chuang SS, et al. Aberrant co-expression of CD19 and CD56 as surrogate markers of acute myeloid leukemias with t(8;21) in Taiwan. Int J Lab Hematol. 2008; 30(2):133–8.
21. Rausei-Mills V, Chang KL, Gaal KK, et al. Aberrant expression of CD7 in myeloblasts is highly associated with de novo acute myeloid leukemias with FLT3/ITD mutation. Am J Clin Pathol. 2008; 129(4):624–9.
22. Jahedi M, Shamsasenjan K, Sanaat Z, et al. Aberrant phenotype in Iranian patients with acute myeloid leukemia. Adv Pharm Bull. 2014;4(1):43–47.

23. Bahia DM, Yamamoto M, Chauffaille M de L, et al. Aberrant phenotypes in acute myeloid leukemia: A high frequency and clinical significance. Haematologica. 2001;86(8):801–6.
24. Breccia M, Porpris MS, Minotti C, et al. Aberrant phenotypic expression of CD15 and CD56 identifies poor prognostic acute promyelocytic leukemia patients. Leuk Res. 2014; 38(2):194–7.
25. Iriyama N, Hatta Y, Takeuchi J, et al. CD56 expression is an independent prognostic factor for relapse in acute myeloid leukemia with t(8;21). Leuk Res. 2013;37(9):1021–6.
26. Abdulateef NAB, Ismail MM, Aljedani H. Clinical significance of co-expression of aberrant antigens in acute leukemia: a retrospective cohort study in Makah Al Mukaramah, Saudi Arabia. Asian Pac J Cancer Prev. 2014;15(1): 221–7.
27. Cui W, Zhang D, Cunningham MT, et al. Leukemia-associated aberrant immunophenotype in patients with acute myeloid leukemia: changes at refractory disease or first relapse and clinicopathological findings. Int J Lab Hematol. 2014;36(6):636–49.

Biography of author(s)

Dr. (Ms). C. C. Kariyawasan (MBBS, Diploma in Pathology, MD in Haematology)
Department of Hematology, Sri Jayewardenepura General Hospital, Sri Lanka.

She was born in 1964 in Colombo, Sri Lanka. She received undergraduate medical training at the North Colombo Medical College, Sri Lanka, and obtained 2nd class honours at the final MBBS. Her postgraduate qualifications include a Diploma in Pathology and an MD in haematology from the Post Graduate Institute of Medicine (PGIM), University of Colombo, Sri Lanka in the year 2002 and 2004 respectively.

Currently, she is a Consultant Haematologist at the Sri Jayewardenepura General Hospital (SJGH) and Post Graduate Training Institute. She has held this post since 2009. Prior to joining SJGH, she was a senior lecturer in Pathology at the Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka for 12 years. She was president of the Sri Lanka College of Haematologists in the year 2015 and a resource person at the Highlights of the American Society of Haematology (ASH) in Asia held in Brisbane in 2016, on the topic of thrombosis.

She has publications in refereed journals on the topics of Multiple Myeloma, Hypereosinophilic syndrome, Immune thrombocytopenic purpura, diabetes mellitus, advanced FBC parameters such as immature platelet fraction and rare findings on flow cytometry analysis. She is currently an examiner for the Diploma and MD in Clinical Haematology examinations conducted by the PGIM. She is a life member of the Sri Lanka College of Haematologists, College of Pathologists of Sri Lanka and the Sri Lanka Medical Association (SLMA). Other interests include music and theatre having performed in more than 35 stage productions, and 10 television productions and for the first time in 2018, presented publicly her own set of plays written and directed by her.

B. L. T. Balasuriya (B.Sc in Medical Laboratory Sciences (Special), M.Phil. (Haematology-reading)
Department of Hematology, Sri Jayewardenepura General Hospital, Sri Lanka.

He was born in Ragama, Sri Lanka on 22nd May 1986. He completed his B.Sc (Special) degree in Medical Laboratory Sciences with 2nd class upper division at the Faculty of Medical Sciences, University of Sri Jayewardenepura in 2012.

He started his career as a Demonstrator at the Department of Allied Health Sciences at the University of Sri Jayewardenepura. Later, He was appointed as a lecturer attached to the Biomedical Science Degree program of the Colombo branch of Management and Science University (MSU), Malaysia. Currently, he is a Medical Laboratory Technologist attached to the Department of Haematology of the Sri Jayewardenepura General Hospital, Sri Lanka since 2016.

He has publications in refereed journals on the topics of Anemia, Multiple myeloma, Hairy Cell Leukaemia, aberrant expression of Acute myeloid leukaemias, Sezary syndrome, and diabetes mellitus. He is a registered Medical Laboratory Technologist of the Sri Lanka Medical Council (SLMC) and the Ceylon Medical College Council (CMCC). He is a member of the College of Medical Laboratory Scientists, Sri Lanka.

S. A. C. D. Ranatunga (B.Sc in Medical Laboratory Sciences (Special), M.Sc in Molecular Pathology)
Department of Hematology, Sri Jayewardenepura General Hospital, Sri Lanka.

He was born in Colombo, Sri Lanka on 29th November 1990. He completed his B.Sc. (Special) in Medical Laboratory Sciences at the Faculty of Medical Sciences, University of Sri Jayewardenepura in 2016 and a Certificate course in Practical skills of Molecular Biology and Genetics at the Institute of Research and Development. He has completed his M.Sc. in Molecular Pathology at the Faculty of Medicine, University of Colombo.

He has been a Medical Laboratory Technologist at the Department of Haematology of the Sri Jayewardenepura General Hospital, Sri Lanka since 2017. He has published several articles in refereed journals on subfertility of males, Multiple myeloma, Hairy Cell Leukaemia, aberrant expression of Acute myeloid leukaemias and Sezary syndrome.

He is a registered Medical Laboratory Technologist of the Sri Lanka Medical Council (SLMC) and the Ceylon Medical College Council (CMCC). He is a member of the College of Medical Laboratory Scientists, Sri Lanka.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Asian Hematology Research Journal, 2(4): 138- 143, 2019.
Available: https://journalahrj.com/index.php/AHRJ/article/view/38

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/984

Chapter 6
Print ISBN: 978-81-976653-0-1, eBook ISBN: 978-81-976653-1-8

Prevalence of Malaria among 1-15-Year Children and the Awareness and Acceptability of Malaria Vaccine in Nsukka Local Government Area, Enugu State, Nigeria

Elijah Sunday Okwuonu [a*], Emmanuel Uzoma Anyaoha [a], Chinaza Blessing Ukwueze [a], Nenrot Sandra Gopep [b,c], Uchenna Athanasius Ubaka [d], Emmanuella Chigozirim Agbedo [a], Chiamaka Lovelyn Nwankwo [a], Patra Chisom Ezeamii [a,c], Ogochukwu Ruth Abasilim [a,e], Blessing Chinenye Amoke [a] and Ikem Chris Okoye [a]

DOI: https://doi.org/10.9734/bpi/dhrni/v1/1171

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1171

ABSTRACT

Background: Malaria is still a serious threat to health, especially for children living in endemic areas. Effective control of malaria requires understanding the local epidemiology and community attitudes towards vaccination and other preventive measures.
Aim: This study was conducted to determine the prevalence of *Plasmodium* infection in children between 1 and 15 years and to evaluate the knowledge and acceptability of the malaria vaccine.
Study Design: Cross-sectional.
Materials and Methods: Prevalence of malaria parasite in 250 children from 1-15 years attending Akulue Memorial Hospital, Nsukka, Enugu State, Nigeria was detected using microscopy. Simultaneously, detailed questionnaires were sent to

[a] *Department of Zoology and Environmental Biology, University of Nigeria, Nsukka, Enugu State, Nigeria.*
[b] *Department of Medicine and Surgery, University of Jos, Plateau State, Nigeria.*
[c] *Department of Public Health/Mph, Georgia Southern University, USA.*
[d] *Department of Parasitology and Entomology, Nnamdi Azikiwe University, Awka, Nigeria.*
[e] *The University of Texas Health Science Center at Houston (UTHealth) School of Public Health, USA.*
**Corresponding author: E-mail: elijah.okwuonu@unn.edu.ng;*

parents/guardians to assess their knowledge and perspectives regarding malaria vaccination.
Results: Of the 250 children examined, 92.4% tested positive for the *Plasmodium* parasite. The malaria prevalence was high (>85%) in the three age groups, (1-5), (6-10), and (11-15) years although they were not significantly different ($p>0.05$). It was not also significantly different between male and female children. This study showed that most parents/guardians were found in favor of introducing a malaria vaccine. The findings highlighted the significance of focused measures to strengthen malaria prevention tactics, such as intensive community education and advocacy efforts to raise vaccination rates.
Conclusion: The results showed that the target children had a high prevalence of malaria infection. Reducing the illness burden among children and attaining sustainable malaria control requires addressing misconceptions and promoting favorable attitudes towards malaria vaccination.

Keywords: Children; malaria prevalence; malaria vaccine; Nigeria.

1. INTRODUCTION

Malaria is a serious public health issue that causes hardships and early mortality in tropical and subtropical nations [1]. It is one of the primary causes of illness and death in children [2]. An estimated one million African children die each year from the primary and secondary effects of malaria infection [3]. The primary cause of hospital admission for children of all ages is malaria complexity, which furthers the ongoing global population reduction [4]. This preventable illness has turned into an epidemic and is still spreading unchecked in many parts of the world [5]. The most vulnerable groups in Africa to malaria are pregnant women and children under five; children who are fatally affected frequently pass away less than 72 hours after exhibiting symptoms [2]. Malaria depletes the necessary nutrients from surviving children, hindering their intellectual and physical development [5]. Over half of the world's population is at risk due to the endemic malaria epidemic, which is present in over 87 countries [6]. In 2022, there were an estimated 249 million cases of malaria worldwide, and 608,000 malaria-related deaths were recorded during that time; Nigeria remains the country with the highest number of cases globally with 66,722,000 cases and 608,000 deaths in 2022 [7]. Since the attack's strength doesn't change yearly or throughout the year, Nigeria's malaria transmission is robust and consistent [8]. A malaria attack episode typically lasts 5-15 days in children between 1-3 years; the child suffers from severe illness with multiple symptoms, including progressive difficulty breathing, frequent vomiting, and convulsions [9]. As a result of this, many households had to spend a lot of money on medications, healthcare, and living expenses. The level of malaria endemicity is determined by ranking the spleen rate in children from 2-9 years old according to severity [10].

In an attempt to reduce and eradicate malaria, a variety of strategies were used, including indoor residual spraying, long-lasting insecticidal nets (LLINs), insecticide-treated bed nets (ITNs), combination therapy based on artemisinin, intermittent preventative treatment during pregnancy (IPTPp), and even more

contemporary strategies like the fast diagnostic test, however, the results were inconsistent, especially in sub-Saharan Africa [11,12]. Weak healthcare systems, widespread corruption, unstable political environments, constant violence, and tribute wars were and continue to be major contributors to these issues [13]. The significant limitations facing the goal of eliminating malaria include changes in female mosquito biting patterns, general insecticide resistance, and the development of multi-drug resistance in the malaria parasite to treatments like chloroquine and other malarial drugs; owing to these restrictions, experts from the pharmaceutical sector, the World Bank, the WHO, and Tropical Disease Research (TDR) have looked into alternate approaches to malaria control, such as vaccination [13].

Vaccines are substances given to stimulate the body's production of antibodies and provide immunity against a disease prepared from the agent that causes the disease or a synthetic substitute. This health policy approach has been successfully used to eradicate an infectious illness and is very effective in controlling disease; over the past 20 years, there has been a major advancement in malaria vaccine development [13]. To better control the disease, the WHO approved the use of RTS, S/AS01, a four-dose malaria vaccine, in October 2021 after a phase III efficacy trial in 7 sub-Saharan African nations [14]. Caregivers' opinions and willingness to accept malaria vaccines need to be determined since Africans usually adopt new medical procedures and technologies later than other populations [13].

Malaria is one risk factor that increases the chance of contracting other illnesses [15]. As a result, it places an immense burden on the nation in terms of the suffering and trauma experienced by its victims, the loss of output, and the expense of therapy [16]. The necessity for coordinated efforts and actions to reverse the situation is highlighted by such a significant burden [17]. Thus, the goal of this research is to comprehend the dynamics of malaria infection in Akulue Memorial Hospital Nsukka, Nigeria. Malaria continues to be a serious global public health issue, especially for vulnerable groups like children. By looking at its prevalence in this age range, specific interventions can be implemented to lower the rates of morbidity and mortality. Awareness of malaria and its preventive measures is crucial. This study helps identify gaps in knowledge, enabling the development of targeted educational campaigns. This empowers communities to adopt and adhere to preventive measures, reducing the overall burden of the disease. Examining the acceptability of malaria vaccines in Nsukka is particularly pertinent due to potential cultural and community-specific factors. Identifying factors influencing vaccine acceptance helps in developing strategies that align with local beliefs and practices, ensuring the successful implementation of vaccination programs. In summary, this study in Nsukka, Nigeria, provides a delicate understanding of malaria dynamics, local awareness levels, and the specific challenges and opportunities for introducing malaria vaccines. The findings can guide policymakers, health practitioners, and community leaders in formulating effective, context-specific strategies for malaria prevention and control.

The study aims to determine the prevalence of malaria in 1-15-year children and their willingness to receive the malaria vaccine in Nsukka LGA, Enugu State,

Nigeria. The specific objectives were to determine the prevalence of malaria among children from 1-15 years in Akulue Memorial Hospital, the prevalence of malaria among 1-5, 6-10, and 11-15-year age groups, the prevalence of malaria in children concerning sex and the awareness regarding malaria vaccines and identify factors that hinder the acceptability of malaria vaccines among parents/guardians in Akulue Memorial Hospital, Nsukka, Nigeria.

2. MATERIALS AND METHODS

2.1 Description of Study Area

Akulue Memorial Hospital is a private hospital established in 1974 by Late Dr. Chukwudi Achufusi to offer healthcare services to the general public, including the wealthy and the poor. It offers comprehensive medical services, including emergency care, surgery, diagnostic testing, treatment for various medical conditions, and specialized care in areas such as cardiology, oncology, pediatrics, etc. The hospital serves people from both far and wide. It's situated at No. 16/18 Akulue Road, Onuiyi, Nsukka, Enugu State, Nigeria.

2.2 Study Design and Population

This study was conducted from February to May 2024. The target population consisted of 250 children from 1-15 attending Akulue Memorial Hospital, Nsukka.

2.3 Data Collection

2.3.1 Sample collection

With the assistance of skilled laboratory personnel, lab scientists, and nurses, venous blood samples were taken from children within the chosen age range using a 2ml syringe. The blood was transferred into EDTA containers filled with anticoagulants to stop the blood from clotting. Samples were immediately examined for the presence of malaria parasites on the day of collection [18]. The remaining samples were stored in a refrigerator which were examined first thing the next day.

2.3.2 Questionnaire administration

A well-structured questionnaire was created to gather information on children's age and gender and analyze the level of awareness and acceptance of the malaria vaccine among caregivers of children in the target age group.

2.4 Malaria Diagnosis

Microscopy was used to make the diagnosis. Currently, the "gold standard" for diagnosing malaria is still microscopy. It is affordable and enables the determination of parasite density and species [19]. Blood samples were placed on glass slides and stained with 3% Giemsa stain, creating thin and thick films [18].

Two microscopists examined the slides; each looked at each specimen separately, and the results were considered affirmative when both microscopists found the same species in each specimen. Once 100 tiny fields were examined, and no parasites were found, the slide was considered negative. If the microscopy revealed the presence of the malaria parasite in at least 100 microscopic fields, the patient was considered positive [20].

2.5 Statistical Analysis

Data were analyzed using Statistical Packages for Social Sciences version 27 (IBM Corporation, Armonk, USA). The prevalence of malaria was estimated by chi-square analysis. Questionnaire responses were summarised as frequency distribution. The threshold for statistical significance was set at $p \leq 0.05$.

3. RESULTS

3.1 Malaria Prevalence in Akulue Memorial Hospital in Children

A total of 250 children were examined for malaria in Akulue Memorial Hospital, Nsukka. Their mean age (±SD) was 6.87±4.36 (range: 1-15 years), and the median age was 6.0 (interquartile range: 7). Among the 250 children, 231(92.4%) were malaria-positive. Prevalence of malaria was high in the three age groups (>85%) examined: 1-5 years, 6-10 years, and 11-15 years. The prevalence of malaria was not significantly different between males and females, nor was it among the three age groups ($p>0.05$) (Table 1). Malaria intensity is presented in Table 2.

Table 1. Prevalence of malaria in children 1-15 years at Akulue Memorial Hospital, Nsukka

Age (year)	Examined	Infected(%)
1-5	104	100(96.2)
6-10	86	78(90.7)
11-15	60	53(88.3)
	250	231(92.4)
		χ^2=3.855, df=3, p=0.146
Sex		
Male	121	111(91.7)
Female	129	120(93.0)
		χ^2=0.147, df=1, p=0.442

3.2 Questionnaire Response of Parents/Guardians of Children Examined for Malaria

The demographics of the parents/guardians who responded to the questionnaires and whose children were examined for malaria are presented in Table 3. Their children were in the age groups 1-5 years 103(41.2%), 6-10 years 87(34.8%), and 11-15 years 60(24.0%). The numbers of males and females were equal, 125(50.0%) each. They were mostly Christians 131(92.4%); and majorly Igbos 226(90.4%).

Table 2. Malaria intensity by categories among 1-15-year children at Akulue Memorial Hospital, Nsukka

Age (year)	Examined	Intensity categories			
		Mild(+)	Moderate(++)	High(+++)	
1-5	100	65(65.0)	34(34.0)	1(1.0)	χ^2=8.619, df=4, p=0.071
6-10	78	54(69.2)	20(25.6)	4(5.1)	
11-15	53	40(75.5)	9(17.0)	4(7.5)	
	231				
Sex					
Male	111	78(70.3)	32(28.8)	1(0.9)	χ^2=5.714, df=2, p=0.075
Female	120	81(67.5)	31(25.8)	8(6.7)	

**5–10,000 (parasites/µl) = mild malaria,*
***10,000–100,000 parasites/µl=moderate malaria*
****100,000 parasites/severe malaria [21]*

Table 3. Demographics of parents/guardians whose children were examined for malaria, at Akulue Memorial Hospital, Nsukka

Demographics	Option	Frequency(%)
Age group (years)	1-5	103(41.2)
	6-10	87(34.8)
	11-15	60(24.0)
Sex	Male	125(50.0)
	Female	125(50.0)
Religion	Christian	231(92.4)
	Muslim	18(7.2)
	Others	1(0.4)
Ethnicity	Igbo	226(90.4)
	Hausa	0(0)
	Yoruba	22(8.8)
	Others	2(0.8)

All the parents/guardians (100%) said their children/wards have suffered malaria at least once in the past. They acknowledged that their children/wards had episodes of fever (100%), and sweating (100%) as some of the symptoms of malaria. Also, 249(99.6%) treated their child/ward malaria symptoms. While 134(53.6%) said they had observed malaria in their homes during the rainy season, as many as 151(60.4%) said they used mosquito nets to protect their sleeping children/wards from mosquito bites (Table 4).

All 250 respondents said they were aware vaccines are being developed for malaria. All also said they had heard about the potential benefits of the vaccines; while 240(96.0%) said they were aware of ongoing trials of malaria vaccines. Almost all the respondents, 247(98.9%) believe that vaccination could be an effective way to prevent malaria. However, 150(60.0%) said they were unaware of the misconceptions and myths surrounding malaria vaccines. All the parents/guardians believed that the malaria vaccine would be a good addition to malaria control in Nigeria (Table 5).

All the parents/guardians were willing to vaccinate themselves against malaria if vaccines became available. They all believe that it is important to vaccinate children against malaria. All but one would recommend vaccinating children in their community against malaria 249(99.6%). However, 14(5.6%) were unwilling to spend more to receive the malaria vaccine, unlike 236(94.4%) who were willing to spend money to receive it. Also, 249(99.6%) believe that the newly discovered WHO-recommended (RTS, S) malaria vaccine for children in 2021 is safe to take (Table 6).

4. DISCUSSION

The results of the study showed that children in the study region, aged 1-15, had a high prevalence of malaria infection. Out of the 250 children examined, 92.4% of

children tested positive for the malaria parasite. This is not similar to a previous study in Anambra State, Nigeria where a lesser proportion (58.2%) was recorded [2]. However, Ligabaw et al. [22] and Osman et al. [23] reported a lower prevalence, indicating that socioeconomic, and environmental factors may be responsible for these differences. The fact that 92.4% of children tested positive for malaria shows that the number of diseases is quite high in the hospital, which may be caused by inadequate control measures. In areas where malaria control measures e.g. insecticide-treated bed nets, and indoor spraying, are not widely used, the risk of malaria infection is higher.

The prevalence of malaria was high in the three age groups (>85%) examined and in contrast to older age groups (6-10; 11-15 years), younger age groups (1-5) had greater prevalence rates. This could be a result of immune system immaturity, signs of variations in exposure, or susceptibility to infection. This is in line with the findings of Nwaorgu and Orajaka [2] that the most vulnerable groups in Africa to malaria are pregnant women and children under five.

Moreover, infection prevalence among the males and females showed that out of 125 male children examined, 111(91.7%) tested positive for malaria, while out of 125 female children examined, 120(93%) tested positive for malaria. Also, out of 125 male children examined, 78(70.3%) tested for mild(+) parasitemia, 32(28.8%) moderate(++) parasitemia, and 1(0.9%) tested high(+++) parasitemia while out of 125 female children examined, 81(67.5%) tested for mild(+) parasitemia, 31(25.8%) moderate(++) and 8(6.7%) tested high(+++) parasitemia. The higher rate of infections in this study among females may reflect variations in exposure or infection susceptibility which may be due to hormonal differences, differences in immune responses, or genetic factors. This is similar to a previous study by Okwuonu et al. [24] which reported that there was a higher prevalence of malaria among females than males. However, the difference is not statistically significant at P=0.442. This also supports the findings of Mbanugo and Ejim [25], who found that there was no significant relationship between sex and prevalence in children. This implies that factors other than gender, such as exposure to mosquitoes, access to healthcare, or immune system factors, may play a bigger role in determining the prevalence of malaria in the population.

Additionally, making the malaria vaccine available can significantly reduce the number of cases and deaths caused by malaria, especially among vulnerable groups such as young children and pregnant women. However, understanding and general opinions about malaria itself, and the effectiveness of a vaccine in controlling and eliminating the disease, will determine how widely accepted malaria vaccines will be. From this study, the majority of parents and guardians who attended the hospital throughout the study were found to be aware of and in favor of the introduction of a malaria vaccine. This was determined after looking into the acceptability and attitudes of these individuals towards the vaccination. This present study confirms the findings of Mtenga et al. [26]. The basic pattern observed in earlier research carried out in some Ghanaian districts by Febir et al. [27] and in other African countries [28] is this positive mentality. This finding is not similar to the previous report by Romore et al. [29] with merely (11%) of people being aware of the upcoming malaria vaccine.

Table 4. Awareness about malaria amongst parents/guardians whose children were examined for malaria, Akulue Memorial Hospital, Nsukka

Variable	Options	Frequency(%)
Has your child ever been diagnosed with malaria?	Yes	250(100)
	No	0(0)
Did your child experience fever within the past month?	Yes	250(100)
	No	0(0)
Have you noticed any symptoms of malaria in your child, such as sweating?	Yes	250(100)
	No	0(0)
Has your child received treatment for malaria in the past year?	Yes	249(99.6)
	No	1(0.4)
Have you observed mosquitoes inside your home during the rainy season?	Yes	134(53.6)
	No	116(46.4)
Do you use mosquito nets to protect your child from bites while sleeping?	Yes	151(60.4)
	No	99(39.6)

Table 5. Awareness about malaria vaccine amongst parents/guardians whose children were examined for malaria, Akulue Memorial Hospital, Nsukka

Variable	Options	Frequency(%)
Are you aware that vaccines are being developed to prevent malaria?	Yes	250(100)
	No	0(0)
Have you heard about the potential benefits of the malaria vaccine?	Yes	250(100)
	No	0(0)
Are you aware of any ongoing clinical trials or research studies related to malaria vaccines?	Yes	240(96.0)
	No	10(4.0)
Do you believe that vaccination could be an effective way to prevent malaria?	Yes	247(98.9)
	No	3(1.2)
Are you familiar with any myths or misconceptions surrounding malaria vaccines?	Yes	150(60.0)
	No	100(40.0)
Do malaria episodes lead to loss of economic productivity?	Yes	246(98.4)
	No	4(1.6)
Will the malaria vaccine be a good addition to the control/eradication policy and program in Nigeria?	Yes	250(100)
	No	0(0)

Table 6. Acceptance of malaria vaccine amongst parents/guardians whose children were examined for malaria, Akulue Memorial Hospital, Nsukka

Variable	Options	Frequency (%)
Are you willing to vaccinate yourself against malaria if a vaccine becomes available?	Yes	250(100)
	No	0(0)
Do you believe that vaccinating children against malaria is important for their health?	Yes	250(100)
	No	0(0)
Would you recommend vaccinating children in your community against malaria?	Yes	249(99.6)
	No	1(0.4)
Will you spend money to receive a malaria vaccine?	Yes	236(94.4)
	No	14(5.6)
Will you encourage your other family members and neighbors to vaccinate their children against malaria?	Yes	249(99.6)
	No	1(0.4)
Do you think the newly discovered WHO recommends malaria vaccine (RTS, S) for children in 2021 is safe to take?	Yes	249(99.6)
	No	1(0.4)
Are you willing to vaccinate yourself against malaria if a vaccine becomes available?	Yes	250(100)
	No	0(0)

Furthermore, the main obstacles to vaccine acceptance from this study were found to be insufficient community involvement, lack of knowledge about the vaccine, worries about the vaccine's negative effects, and ineffective vaccination service delivery. This is similar to the report of Dimala et al. [30] in community engagement was found to be the most frequently stated challenge. From this study, it's also observed that the acceptability of malaria vaccination remains severely limited due to concerns about vaccine side effects which is in line with results obtained from Bingham et al. [28], Ojakaa et al. [31] and Mtenga et al. [26]. In the past, vaccination has been linked to the spread of other illnesses, as the polio vaccine in northern Nigeria demonstrated by Ghinai et al. [32]. This will make parents, guardians, or caregivers who are fearful of potential side effects less likely to accept a malaria vaccine, even if it's proving to be safe and effective. This may hinder the acceptability of the malaria vaccine, making it less effective in preventing disease. According to this report, about 5.6% of the respondents expressed doubts about the vaccines' cost if households must pay for them. This confirms the report of Hung et al. [33] that the cost and affordability of certain health interventions have been linked to non-compliance, particularly in low-resource areas, which has reduced the success achieved in the control of diseases like malaria. Besides, initiatives that come at no expense to the general public have produced better outcomes. As a result, this aspect needs to be taken into account before developing and implementing malaria vaccination treatments. According to the previous study by Chukwuocha et al. [34], getting the support of household heads is particularly important because they typically foot the bill for family medical needs. These findings are consistent with those reported by Abdulkadir and Ajayi [35] which showed that the majority of those who said they would not get vaccinated said it was because their husbands would not approve of it.

5. CONCLUSION

The results showed that the target children had a high prevalence of malaria infection. Despite the significant illness burden, parents/guardians exhibit encouragingly high levels of awareness and acceptability of the malaria vaccine. This positive response indicates that there is a good chance that vaccination programs will be implemented successfully. To enhance the impact of these findings, it is essential to maintain and improve educational campaigns to ensure sustained awareness and acceptance of the vaccine. Additionally, addressing any doubts about the safety and effectiveness of vaccines will also be essential to preserving high levels of acceptance and trust. Addressing issues regarding the costs of acquiring the vaccine and getting it to the most vulnerable populations especially children and pregnant women, is important to overcome challenges and facilitate the rollout of malaria vaccines. Strengthening healthcare infrastructure to support consistent vaccine delivery and monitoring will further reduce malaria incidence and improve overall child health outcomes. Maintaining already existing malaria intervention programs is important to reduce vector populations and protect individuals when the rollout begins.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of manuscripts.

CONSENT

Written and Oral informed consent was obtained from the parents/guardians of all the individual participants to ascertain their willingness to participate in this study.

ETHICAL APPROVAL

An introductory letter was collected at the University of Nigeria, Nsukka, Zoology and Environmental Biology Department. With the letter, Ethical approval was obtained from the Enugu State Ministry of Health Ethics Committee with *Ref NO*.: MH/MSD/REC21/512 after the proposal was internally reviewed. To facilitate the quick recruitment of study subjects, informed permission was obtained from the medical director and head of the laboratory. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

ACKNOWLEDGEMENTS

We're grateful to the Medical Director, nurses, and laboratory scientists of Akulue Memorial Hospital, Nsukka, for their assistance. We're also grateful to all study participants and their parents/guardians.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

REFERENCES

1. Cheesbrough M. District laboratory practice in Tropical Countries. examination of blood for malaria parasites. Cambridge University Press; 1998.
2. Nwaorgu OC, Orajaka BN. Prevalence of malaria among children 1-10 years old in communities in Awka North Local Government Area, Anambra State South East Nigeria. African Research Review. 2011;5(5):264-281.
3. Fawole OI, Onadeko MO. Knowledge and management of malaria in under-five children by primary health care workers in Ibadan South East Local Government Area. Nigeria. Post Graduate Medical Journal. 2001;8(1):1-5.
4. Marotta C, Di Gennaro F, Pizzol D, Madeira G, Monno L, Saracino A, Moccia L. The at-risk child clinic (ARCC): 3 years of health activities in support of the most vulnerable children in Beira, Mozambique. International Journal of Environmental Research and Public Health. 2018;15(7):1350.

5. WHO. Roll Back Malaria: Project for Accelerated 14. Implementation of Malaria Control Africa 1997-1998. 1998;9.
6. WHO. Malaria; 2019.
Available:https://www.who.int/news-room/fact-sheets/detail/malaria
Accessed on 29th January 2024.
7. WHO. World Malaria Report 2023; 2023.
Available:https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2023
Accessed on 20 January 2024.
8. Ukwubile CA, Krustu T, Samagoro CT. Prevalence of malaria parasite in Takum Local Government Area, Taraba State, Nigeria. Journal of Bacteriology Mycology Open Access. 2018;6(1):53-55.
9. Ezenwelu UF. Malaria prevalence among children in Abuja. South American Journal of Public Health, Special Edition. 2016;1-6.
10. WHO (2020). Fact sheet malaria; 30 November 2020.
Available:https://www.who.Int/newsroom/fact-sheets/detail/malaria
11. WHO World Malaria Report. Geneva, World Health Organization. 2014. Report; 2014.
Available:https://www.who.int/malaria/world_malaria_report_2014/en/
Accessed on 29th January 2024.
12. Ali A, Bala AY, Okwuonu ES, Orakwelu CH, Aguzie IO. Reduction of malaria by insecticide-treated mosquito nets in Potiskum, Yobe State, Nigeria. International Journal of Tropical Disease & Health. 2020;41(20):1-10.
Available:https://journalijtdh.com/index.php/IJTDH/article/view/1057
13. Onyekachi O, Abana C, Chioma O, Nwajiobi F. Prevalence of malaria and willingness to accept malaria vaccine amongst Parents, Guardians, and Caregivers of Children under 5 Years; 2021.
Available:https://globalpresshub.com/index.php/ARJOCS/article/view/1056
14. WHO. WHO Recommends Groundbreaking Malaria Vaccine for Children at Risk; 2022.
Available:https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk
Accessed on 18 January 2024.
15. Boraschi D, Abebe N, Alemayehu M, Aseffa A, Chiodi F, Chisi J, Del Prete G. Immunity against HIV/AIDS, malaria, and tuberculosis during co-infections with neglected infectious diseases: Recommendations for the European Union research priorities. PLoS Neglected Tropical Disease. 2008;2(6):e255.
16. Onwujekwe OE, Chima RI, Okonkwo PO. Economic burden of malaria illness versus that of a combination of other illnesses. A Study in Five Malaria Holo-Endemic Communities. Health Policy. 2000;54:143-159.
17. Anaebonam E, Eze CC, Okeke CE, Nweze KE, Okemadu CO. Prevalence and intensity of malaria infection and associated risk factors in Anambra State, Nigeria. World Journal of Biology Pharmacy and Health Sciences. 2021;7(3):030-045.
18. Cheesbrough M. District laboratory practice in Tropical Countries Part 2. New York: Cambridge University Press. 2006;300-301.

19. WHO. Parasitological confirmation of malaria diagnosis. Geneva: World Health Organization; 2009. Google Scholar.
Accessed on 29th January 2024.
20. Berzosa P, de Lucio A, Roman-Barca M, Herrador Z, Gonzalez V, Garcia L, et al. Comparison of three diagnostic methods (microscopy, RDT, and PCR) for the detection of malaria parasites in representative samples from Equatorial Guinea. Malaria Journal. 2018;17(1):133.
Available:https://rdcu.be/dyme8
21. Wilairatana P, Tangpukdee N, Krudsood S. Definition of hyperparasitemia in severe falciparum malaria should be updated. Asian Pacific Journal of Tropical Biomedicine. 2013;3:7.
Available:https://doi.org/10.1016/S2221-1691(13)60119-7
22. Ligabaw W, Demekech D, Mengistu E, Sisay G, Mulugeta A. Asymptomatic malaria and associated risk factors among school children in Sanja Town, Northwest Ethiopia. Hindawi Publishing Corporation International Scholarly Research Notice. 2014;2014:6.
23. Osman NK, Gideon K, Helegbe PAA, Abass A, Frank A, Zulka Z, Evans DA. Prevalence of asymptomatic malaria among children in the tamale metropolis: How Does the PfHRP2 CareStart™ RDT Perform against Microscopy? Hindawi Journal of Tropical Medicine. 2019;7.
Available:https://www.doi.org/10.1155/2019/6457628.
24. Okwuonu ES, Obiomalemoha AM, Ubaka UA, Eze FC, Mgboji OA, Okeke OA, et al. Prevalence of Malaria Parasites among Children from 1 – 15 Years of Age at Bishop Shanahan Hospital Nsukka Enugu State, Nigeria. South Asian Journal of Parasitology. 2023;6(3):135-146.
25. Mbanugo JI, Ejim DO. Plasmodium infections in children aged 0-5yrs in Awka Metropolis, Anambra State, Nigeria. Nigerian Journal of Parasitology. 2000;21:55-59.
26. Mtenga S, Kimweri A, Romore I, Ali A, Exavery A, Sicuri E, et al. Stakeholders' opinions and questions regarding the anticipated malaria vaccine in Tanzania. Malaria Journal. 2016;15:189.
Available:https://www.doi.org/10.1186/s12936-016-1209-6PMID:27048260
27. Febir LG, Asante KP, Dzorgbo DS, Senah KA, Letsa TS, Owusu-Agyei S. Community perceptions of a malaria vaccine in the Kintampo districts of Ghana. Malaria Journal. 2013;12:156.
Available:https://doi.org/10.1186/1475-2875-12-156.
28. Bingham A, Gaspar F, Lancaster K, Conjera J, Collymore Y, et al. Community perceptions of malaria and vaccines in two districts of Mozambique. Malaria Journal. 2012;11:394.
29. Romore I, Ali AM, Semali I, et al. Assessment of parental perception of malaria vaccine in Tanzania. Malaria Journal. 2015;14:355.
Available:https://doi.org/10.1186/s12936-015-0889-7
30. Dimala CA, Kika BT, Kadia BM, Blencowe H. Current challenges and proposed solutions to the effective implementation of the RTS, S/AS01 Malaria Vaccine Program in sub-Saharan Africa: A systematic review PLoS ONE. 2018;13(12):e0209744.
31. Ojakaa DI, Jarvis JD, Matilu MI, Thiam S. Acceptance of a malaria vaccine by caregivers of sick children in Kenya Malaria Journal. 2014;13:172.

32. Ghinai I, Willott C, Dadari I, Larson HJ. Listening to the rumors: What the Northern Nigeria polio vaccine boycott can tell us ten years on. Global Public Health. 2013;8(10):1138-1150.
33. Hung LQ, De Vries PJ, Giao PT, Nam NV, Binh TQ, Chong MT, Quoc N.T. Control of malaria: A successful experience from Vietnam. Bulletin of the World Health Organization. 2002;80:660-666.
34. Chukwuocha UM, Okorie PC, Iwuoha GN, Ibe SN, Dozie IN, Nwoke BE. Awareness, perceptions, and intent to comply with the prospective malaria vaccine in parts of South Eastern Nigeria. Malaria Journal. 2018;17(1):187. Available:https://www.doi.org/10.1186/s12936-018-2335-0-PMID:29720172.
35. Abdulkadir BI, Ajayi IO. Willingness to accept malaria vaccine among caregivers of under-5 children in Ibadan North Local Government Area, Nigeria. Malaria World Journal. 2015;6:2.

Biography of author(s)

Elijah Sunday Okwuonu
Department of Zoology and Environmental Biology, University of Nigeria, Nsukka, Enugu State, Nigeria.

Research and Academic Experience: He is a lecturer at the Zoology and Environmental Biology Department, University of Nigeria. He has supervised many undergraduate students' projects and attended many conferences. Currently, he is undergoing a project entitled "Parasites' diversity and conservation of cave-dwelling bats in Enugu State, Nigeria" for his doctoral research.

Research Specialization: His research areas mainly include parasitology and public health, community and conservation ecology, epidemiology and one health, entomology and environmental biology.

Number of Published papers: He has published 24 articles in several journals.

Special Award: He was awarded a 2019 Small Mammals Conservation Organization Fellowship, the 2022 Bat Conservation International Student Research Scholarship, and the 2023 Ist Rufford Small Grant.

Any other remarkable point(s): He is a member of many academic societies.

Emmanuel Uzoma Anyaoha
Department of Zoology and Environmental Biology, University of Nigeria, Nsukka, Enugu State, Nigeria.

He developed a profound interest in the natural sciences and a deep concern for public health issues, particularly those affecting vulnerable populations. This passion led him to pursue a degree in Zoology and Environmental Biology at the University of Nigeria, where he recently graduated. He plans to pursue further studies and contribute to global efforts to combat malaria and other infectious diseases. With his strong academic background, hands-on research experience, and unwavering commitment to improving health outcomes, he is well-equipped to make significant contributions to the field of public health.

Chinaza Blessing Ukwueze
Department of Zoology and Environmental Biology, University of Nigeria, Nsukka, Enugu State, Nigeria.

She is a young woman with a deep passion for nature. This blossomed into a strong desire to understand and protect the environment leading her to pursue a degree in Zoology and Environmental Biology. She

participated as a volunteer in a research work titled "Parasites' diversity and conservation of cave-dwelling bats in Enugu State, Nigeria", where she assisted in cave bat sampling, data collection, and conservation outreaches. In 2021, she was graduated from the University of Nigeria with a Bachelor's degree in Zoology and Environmental Biology. She is passionate about addressing health disparities and contributing to the global fight against parasitic diseases.

Nenrot Sandra Gopep
Department of Medicine and Surgery, University of Jos, Plateau State, Nigeria.
Department of Public Health/Mph, Georgia Southern University, USA.

She is a dedicated medical professional passionate about public health. She earned her MBBS from the University of Jos, Nigeria. She is currently a research assistant at Georgia Southern University, where she is pursuing her MSc in Public Health. She has extensive research experience, participating in studies on fetal lung maturation, schizophrenia, tactical athletes, infectious diseases, and child street hawking. She volunteered with the Hope Hill Foundation, the Center for Family Health Initiative, etc. Her interest in public health was sparked by personal experiences, including vaccine-preventable diseases.

Uchenna Athanasius Ubaka
Department of Parasitology and Entomology, Nnamdi Azikiwe University, Awka, Nigeria.

He is a Lecturer in the Department of Parasitology and Entomology, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria. His areas of interest include Public Health Parasitology and Medical Entomology. He has published numerous papers in the areas and attracted Nigerian TETFUND funding to pursue further studies in the area of Parasitology and Public Health. Currently, he has ongoing research that focuses on Parasitic Helminths and Malaria-Typhoid Co-infection.

Emmanuella Chigozirim Agbedo
Department of Zoology and Environmental Biology, University of Nigeria, Nsukka, Enugu State, Nigeria.

She is a cutting-edge researcher and recent graduate from the University of Nigeria, where she earned her BSc in Zoology and Environmental Biology. Throughout her studies, she developed a strong interest in the conservation of ecosystems focusing on the prevalence and diversity of intestinal and haemoparasites in squirrels. She has volunteered at educational outreaches and community service.

Chiamaka Lovelyn Nwankwo
Department of Zoology and Environmental Biology, University of Nigeria, Nsukka, Enugu State, Nigeria.

She is a graduate from the University of Nigeria where she obtained a B.Sc. degree in Zoology and Environmental Biology. She has been actively involved in animal research and is a research volunteer to research with Mr. Elijah Okwuonu for her PhD work. Her research interest is rooted in parasitology, animal physiology, and public health. She is passionate about human health and animal science because of its tremendous importance. Her research mainly focuses on understanding disease transmission, prevention and treatment in animals is essential for safeguarding public health and preventing the spread of zoonotic diseases.

Patra Chisom Ezeamii
Department of Zoology and Environmental Biology, University of Nigeria, Nsukka, Enugu State, Nigeria.
Department of Public Health/Mph, Georgia Southern University, USA.

She is a Nigerian public health enthusiast passionate about infectious disease surveillance and pandemic preparedness. Her commitment to public health solidified during her university final year project on malaria prevalence and drug resistance. She volunteered at Family Health International, assisting with COVID-19 surveillance. She also worked part-time at the National Arbovirus and Vector Research Center of Nigeria. She is enrolled in a Master's degree in Public Health program at Georgia Southern University, focusing on emerging infectious disease surveillance and modeling. She has several publications in reputed journals.

Ogochukwu Ruth Abasilim
Department of Zoology and Environmental Biology, University of Nigeria, Nsukka, Enugu State, Nigeria.
The University of Texas Health Science Center at Houston (UTHealth) School of Public Health, USA.

She obtained her Bachelor's degree in Zoology and Environmental Biology from the University of Nigeria. There, she honed her research skills as a research assistant under Mr. Elijah Okwuonu. This early exposure to research ignited her curiosity and solidified her commitment to a career focused on improving public health on a broader scale. Currently, she is pursuing a Master of Public Health at the University of Texas Health Science Center, Houston, US. As a teaching assistant, she demonstrates her dedication to learning and sharing her expertise with others. Her research interests encompass various public health areas like global health, nutrition epidemiology, maternal and child health, and chronic diseases.

Blessing Chinenye Amoke
Department of Zoology and Environmental Biology, University of Nigeria, Nsukka, Enugu State, Nigeria.

She obtained her BSc in Zoology and Environmental Biology at the University of Nigeria, where she worked on epidemiological study of intestinal helminths among schoolchildren. This developed her interest in Parasitology and Public Health. During her undergraduate days, she volunteered to assist Mr. Elijah Okwuonu in conducting her PhD research. Currently, she is pursuing her Master's degree in Parasitology and Public Health at the same institution and working with Union Bank of Nigeria as a Direct Sales Agent.

Ikem Chris Okoye (Professor)
Department of Zoology and Environmental Biology, University of Nigeria, Nsukka, Enugu State, Nigeria.

He is a Professor of Parasitology and Public Health at the University of Nigeria, Zoology and Environmental Biology Department. He has been studying Entomology, Parasitology, and Public Health for more than 4 decades. He is well-published in reputable journals and book chapters. He has supervised many undergraduate and postgraduate students. He is the former Head of the Department of Zoology and Environmental Biology. He has many collaborations and won several awards. He is the founder of the Society of Animal and Environmental Biology.

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1171

Chapter 7
Print ISBN: 978-81-976653-0-1, eBook ISBN: 978-81-976653-1-8

COVID-19 Vaccine-induced Parsonage-turner Syndrome: A Case Study

Mohammad Asim Amjad [a*], Zamara Hamid [b], Yamini Patel [c], Mujtaba Husain [c], Ammad Saddique [c], Adnan Liaqat [d] and Pius Ochieng [e]

DOI: https://doi.org/10.9734/bpi/dhrni/v1/1189

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1189

ABSTRACT

The risk of neurological adverse effects is present in all contemporary vaccines. Parsonage-Turner syndrome (PTS), an uncommon peripheral nerve condition associated with coronavirus disease 2019 (COVID-19) immunization, has been reported in only a few cases. A concise literature review and the case of a 78-year-old male with no recent trauma or infection presented with chest pain and bilateral hand weakness following COVID-19 vaccination. 21 days following the initial dose, the patient received a second dose of the BNT162b2 COVID-19 vaccine three weeks before the onset of symptoms. The physical examination revealed significant weakness in the right-hand grasp and wrist flexion. The diagnostic workup revealed no underlying diabetes mellitus, infections, or other autoimmune diseases. The bilateral first dorsal interosseous and right deltoid, biceps, and triceps muscles exhibited decreased motor unit recruitment in nerve conduction investigations, including needle electromyography, confirming PTS. Occupational therapy and oral prednisone were administered to preserve the patient's range of motion. The pathophysiology and etiology of PTS are not entirely comprehended. Various factors, including genetic, environmental, and immunological predisposition, may contribute to the development of the syndrome. Infections, vaccines, and injuries are the most common causes of non-hereditary forms. No test can definitively corroborate or disprove the existence of PTS. Imaging modalities and electrodiagnostic studies are instrumental in eliminating alternative differential diagnoses.

---

[a] Pulmonary and Critical Care Medicine, The University of Texas Science Center at Houston, Houston, Texas, USA.
[b] Internal Medicine, Shifa International Hospital, Islamabad, Pakistan.
[c] Internal Medicine, The Wright Center for Graduate Medical Educations, Scranton, PA, USA.
[d] Pulmonary and Critical Care Medicine, Mclaren Health/Michigan State University, Lansing, MI, USA.
[e] Pulmonary and Critical Care Medicine, Geisinger Community Medical Center, Scranton, PA, USA.
**Corresponding author: E-mail: muhammadasimamjad@gmail.com;*

Keywords: Post covid vaccination parsonage-turner syndrome; COVID-19; neuralgic amyotrophy; sars-cov-2 vaccines; acquired peripheral neuropathy.

1. BACKGROUND

In 1948, Parsonage et al. identified Parsonage-Turner syndrome through case investigations. This disease is also known as neuralgic amyotrophy. The nature of the disease is episodes of neuropathic pain followed by rapidly progressive multifocal paresis and atrophy of the muscles of the upper limbs. The disease has a prolonged relapsing prognosis with episodes separated by years of recovery [1,2]. The first-ever case that developed after vaccination was described by Rigal et al. in [3].

2. CASE PRESENTATION

A 78-year-old non-smoker male with a medical history of coronary artery disease presented with constant,non-exertional, right-sided chest pain for one hour and a new onset of bilateral hand weakness for three days. He had no history of neurological disease or allergies and denied any recent trauma or infection [4].

The patient received a second BNT162b2 COVID-19 vaccine 21 days after the first dose, three weeks before the onset of these symptoms. The physical examination revealed a substantial weakness in the right-hand grip and wrist flexion (*Medical Research Council grade 3*). There were no additional motor or sensory deficits, bulbar weakness, or upper motor neuron dysfunction indications.

2.1 Investigations

The diagnostic workup for the underlying acute coronary syndrome, infections (CMV, EBV, HIV, Mycoplasma, and Lyme disease), and rheumatological illnesses (ANA, rheumatoid factor, SSA/SSB, and ANCA) all came back negative. The imaging workup, which included magnetic resonance imaging (MRI) of the head, cervical spine, and thoracic spine, was performed with and without contrast and revealed no demyelination, fracture deformity, traumatic subluxation, or compressive myelopathy (Fig. 1). The patient was found to have left lower trunk brachial plexopathy, including bilateral median neuropathies at the wrist and ulnar sensory neuropathy as per nerve conduction studies. In addition, a decrease in motor unit activation was observed in the bilateral first dorsal interosseous muscles and the right deltoid, biceps, and triceps muscles, as demonstrated by needle electromyography (Tables 1-3) [4].

2.2 Differential Diagnosis

- Mononeuritis multiplex
- Motor neuropathy
- Entrapment neuropathies
- Cervical radiculopathy, degenerative
- Tick-borne illness
- Peripheral Nerve Tumor

Table 1. Sensory nerve conduction study findings

Nerve/sites	Recruitment Site	Onset latency ms	Peak latency ms	Reference ms	NP amplitude ms	Reference µV	Segments	Distance ms	Velocity m/s	Reference m/s
L median- Digit 11 (antidromic)										
Wrist	Digit	3.5	4.4	>3.6	7.4	>15.0	Wrist-Digit II	130	37	>56
R median- Digit 11 (antidromic)										
Wrist	Digit 11	2.85	3.5	<3.6	7.5	>15.0	Wrist – Digit II	130	46	>56
L ulnar – Digit V (antidromic)										
Wrist	Digit V	2.6	3.2	<3.1	6.2	>10.0	Wrist – Digit V	110	49	>54
R ulnar – Digit V (antidromic)										
Wrist	Digit V	2.6	3.2	<3.1	1.9	>10.0	Wrist – Digit V	110	43	>54
L radial – anatomical snuffbox (forearm)										
Forearm	Wrist	1.8	2.5	<2.9	20.9	>20.0	Forearm – wrist	100	56	>49
R radial – anatomical snuffbox (forearm)										
Forearm	Wrist	1.5	2.2	<2.9	21.2	>20.0	Forearm – wrist	100	69	>49
L median, ulnar–transcarpal comparison										
Median palm	Wrist	2.3	3.1	<2.3	24.6	>50	Median palm - wrist	80	35	>56
Ulnar palm	Wrist	1.4	2.0	<2.3	8.8	>15.0	Median palm - wrist	80	59	>56
R median, ulnar–transcarpal comparison										
Median palm	Wrist	2.1	2.8	<2.3	21.9	>50.0	Median palm - wrist	80	38	>56
Ulnar palm	Wrist	1.4	2.2	<2.3	3.0	>15.0	Median palm - wrist	80	59	>56

- *Bilateral median sensory nerve action potential (SNAP) amplitudes are diminished, peak latency is prolonged on the left and normal on the right.*
- *Bilateral ulnar sensory nerve action potential (SNAP) amplitudes are diminished severely on the right; peak latencies are borderline.*
- *Bilateral radial sensory nerve action potential (SNAP) amplitudes are borderline, and peak latencies and conduction velocities are normal.*
- *Bilateral ulnar compound muscle action potential (CMAP) amplitudes and distal latencies are normal.*

L - left; R – right

(The coauthor generated the figure completely for this publication and gained agreement from the patient to post it)

Table 2. The motor nerve conduction study revealed no significant changes

Nerve/Sites	Latency ms	Reference ms	Amplitude mV	Reference mV	Relative amplitude %	Duration ms	Segments	Distance mm	Latency difference ms	Velocity m/s	Reference m/s
L median - APB											
Wrist	4.5	≤4.5	3.0	≥4.0	100	5.0	Wrist – APB	70			
Elbow	9.6		2.8		93.2	5.1	Elbow – Wrist	240	5.1	47	≥48
Ulnar Wrist	3.2		2.1		76.4	6.4					
Ulnar Elbow	9.4		1.8		7.2	7.2					
R Median – APB											
Wrist	4.0	≤4.5	5.0	≥4.0	100	6.8	Wrist – APB	70			
Elbow	8.5		4.9		98.1	7.2	Elbow – Wrist	235	4.5	52	≥48
L Ulnar – ADM											
Wrist	2.8	≤3.6	10.0	≥6.0	100	6.4	Wrist – ADM	65			
B.Elbow	7.0		9.3		93.9	6.7	B.Elbow – Wrist	230	4.2	51	≥51
A.Elbow	9.0		9.0		99.9	6.9	A.Elbow – Wrist	330	6.2	49	≥51
							A.Elbow- B.Elbow	100	2.2	45	≥51
R Ulnar – ADM											
Wrist	3.5	≤3.7	11.5	≥7.0	100	5.3	Wrist - FDI				
B.Elbow	7.8		10.7		93.4	5.7	B.Elbow – Wrist	230	4.2	55	≥51
A.Elbow	9.7		10.7		99.3	5.8	A.Elbow – Wrist	330	6.2	53	
							A.Elbow- B.Elbow	100	2.0	51	≥51
R Ulnar – FDI											
Wrist	3.3	≤3.7	13.3	≥7.0	100	5.2	Wrist – FDI				
B.Elbow	7.8		12.2		91.9	5.6	B.Elbow – Wrist	230	4.5	51	≥51
A.Elbow	9.9		11.5		94.6	5.7	A.Elbow – Wrist	330	6.7	50	
							A.Elbow- B.Elbow	100	2.2	46	≥51

L - left; R - right; APB - abductor pollicis brevis; ADM - abductor digiti minimi; FDI - first dorsal interosseous (muscle); A - above; B – below
(The coauthor generated the figure completely for this publication and gained agreement from the patient to post it)

Table 3. Electromyography reveals decreased motor unit recruitment in the affected region's hallmark for Parsonage-Turner Syndrome (bilateral first dorsal interosseous and right deltoid, biceps, and triceps muscles)

Insertional		Spontaneous			MUAP					Additional
Muscle	**Activity**	**Fibrillation/PSW**	**Fasciculation**	**Other**	**Duration**	**Amplitude**	**Polyphasic**	**Recruitment**	**Activations**	**Comments**
L first dorsal interosseous	Normal	None	None	None	N	1	None	Reduced	Normal	Mild
R deltoid	Normal	1	Few	None	1	2	3	Reduced	Normal	Moderate
R biceps brachii	Normal	None	None	None	2	2	3	Reduced	Normal	Moderate to severe
R triceps brachii	Normal	None	None	None	N	1	None	Reduced	Normal	Mild
R flexor carpi ulnarsi	Normal	None	None	None	N	Normal	1	Reduced	Normal	Mild
R flexor dorsal interosseous	Normal	None	None	None	N	-1	2	Single unit	Normal	

L - left; R - right; MUAP - motor unit action potential; PSW - positive sharp waves

(The coauthor generated the figure completely for this publication and gained agreement from the patient to post it)

2.3 Treatment

The patient was treated with 40 mg/day oral prednisone and occupational therapy to maintain range of motion and activities of daily living.

2.4 Outcome and Follow-up

He showed significant improvement in pain, with a slight recovery from his weakness. He was then discharged with regular outpatient follow-ups to observe the disease course and taper steroids.

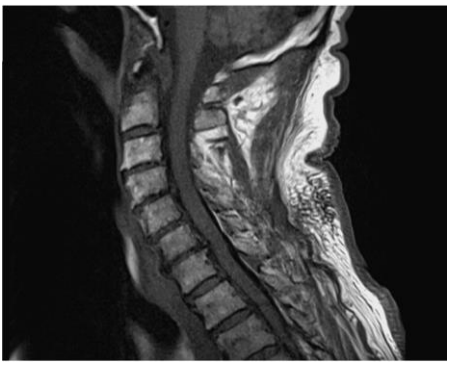


Fig. 1. MRI of the cervical spine showing multilevel degenerative disc disease and no signs of demyelination, fracture deformity, traumatic subluxation, or compressive myelopathy
(The coauthor generated the figure completely for this publication and gained agreement from the patient to post it)

3. DISCUSSION

PTS is also known as neuralgic amyotrophy, brachial plexus neuritis, brachial plexopathy, and shoulder-girdle syndrome. Parsonage et al. were the pioneers who described 136 cases of brachial plexus neuropathy or its synonyms in 1948 [1]. Over the years, several publications have been published on the clinical spectrum of PTS. Van Alfen provided a very detailed case series involving 246 individuals in a healthcare setting [2,4]. They characterized the clinical symptoms of this disease process, which included acute, unrelenting, asymmetrical neuropathic pain in the upper extremities. This pain may evolve into neurological abnormalities such as weakening and paresthesia, typically found in the distribution of specific nerves.

PTS can be categorized into non-hereditary and hereditary variants. In around 85% of instances, the latter variant is caused by a mutation of the SEPT9 gene on chromosome 17q25 [2,5]. The prevalence is higher in males, accounting for 68% of cases, with an estimated occurrence of two to four instances per 100,000

individuals annually [5,6]. Rigal et al. were the first to document PTS occurring after immunization [3]. Most occurred after polio, chickenpox, hepatitis B, influenza, and HPV immunizations [7–9]. However, post-vaccination PTS is an infrequent entity, with only 4.3-15% of all cases attributed to vaccines [6]. Similar cases have been reported with the advent of the COVID-19 pandemic and the initiation of a robust global vaccination drive [4].

PTS is a specific type of peripheral neuropathy targeting the nerves outside the central nervous system. PTS encompasses a diverse range of clinical manifestations. Typically, the patient experiences intense pain in the upper extremities, followed by neurological impairments. During the attack, the extent and distribution of the affected peripheral nerve's pathology vary, including lumbosacral plexus, phrenic nerve, and recurrent laryngeal nerve [2,6–10].

The causes and mechanisms of PTS are not completely understood. Multiple factors, including genetic, environmental, and immunological predisposition, can contribute to the development of the condition. Most instances are caused by an autoimmune reaction, which can be triggered by infections or environmental factors. This response leads to inflammation of specific peripheral neurons due to the infiltration of lymphocytes. As a result, the nerves undergo degeneration and become constricted [2,6,10–14].

Table 4 indicates the most common triggering factors described in the previous studies. Some researchers hypothesized that certain individuals have a genetic predisposition to acquiring PTS after being exposed to the stated events. An individual with a genetic predisposition may not show symptoms of the disease unless they encounter environmental or immunological factors that cause it to become active [15–19].

Vaccines trigger strong immunological responses throughout the body that may lead to an autoimmune reaction, perhaps causing PTS. Post-vaccination neuralgic amyotrophy develops within four weeks of its administration. Patients can present with symptoms in the contralateral to the injected region, indicating that PTS is unlikely to be attributable to direct nerve injury from the immunization [15,16]. Our literature review yielded seven reported cases following COVID-19 vaccination, which we have summarized along with our case here [20,21,4].

Currently, the following COVID-19 vaccines have been authorized by the FDA.

1. Pfizer-BioNTech (Comirnaty): Suitable for individuals aged 16 and older.
2. Moderna: Suitable for individuals 18 years of age or older.
3. Janssen/Johnson & Johnson: Suitable for individuals aged 18 and older.
4. Novavax: A revised formula has been approved for use in individuals aged 12 and older to provide enhanced protection against circulating variants.

More than 7 billion people worldwide have received at least one dose of the COVID-19 vaccine, including 417.80 million in the United States [22]. For neuralgic amyotrophy and brachial neuritis, the Vaccine Adverse Event Reporting System (VERS) yielded 60 reports (mRNA-1273 (29), BNT162b2 (30), and J&J (1) [23]. The system is subject to significant limitations, including underreporting cases and reporting bias, as it is accessible to the general population.

Our assessment of cases revealed a clear gender bias, with most patients being male. The average age at the time of diagnosis was 52, with the youngest patient being identified at the age of 35 years (Table 5). Pain was the most prevalent symptom in all these instances, but its location varied. Our case was unique, as he presented us with atypical chest pain. In most instances, there were sensory complaints such as paresthesia or numbness, depending on which peripheral nerves were damaged [2,16].

Currently, no test definitively confirms or rules out the presence of PTS. Electrodiagnostic investigation and imaging modalities such as MRI and ultrasound eliminate other possible diagnoses [16,24]. PTS is considered a type of injury that affects the axons, and needle electromyography can help determine and evaluate the extent of axonal damage and reinnervation. Electromyography requires a meticulous focus on the muscles of the upper limb. Across all these studies, including our own case report, there was a noticeable reduction in the activation of motor units in the afflicted muscles (Fig. 1). In addition, MR neurography and high-resolution ultrasonography are highly useful diagnostic instruments [11–14,18]. Two of the cases by Sophie depicted their significance in early detection [20].

Table 4. Common causes of parsonage-turner syndrome [15–19]

1. Idiopathic
2. Hereditary
3. Infection (Viral, Bacterial, Parasitic)
4. Brachial Plexus Surgery
5. Unaccustomed Strenuous Exercise
6. Minor Trauma
7. Anesthesia
8. Rheumatological Diseases
9. Vaccinations (Influenza, HPV, tetanus, Hepatitis B, Typhoid)
10. Autoimmune Disorders (PAN, Lupus, Temporal Arteritis)

PTS has no specific treatment, as it might resolve independently without intervention [24]. Supportive pain management techniques, such as non-steroidal anti-inflammatory medications and opiates, are effective during acute periods. Most patients are managed conservatively. Several researchers suggest the early use of oral prednisone in the early stages of the condition since it can aid in reducing the progression of the disease and promote early recovery [25]. Following the occurrence of acute neuropathic pain, several medical experts suggest the utilization of co-analgesics (such as amitriptyline, carbamazepine, and gabapentin) as an alternative to steroids to mitigate the negative consequences associated with steroid usage [24,26,27]. Out of the eight cases that were studied, six were administered oral prednisone, while the other two were prescribed gabapentin. Each of them had substantial improvement in symptoms. Furthermore, physical rehabilitation therapy has a role in managing muscular weakness by preserving both muscle strength and the range of motion in the joints. Surgery, namely nerve decompression and rebuilding, may be an option for certain patients who do not respond to other treatments. It is most effective when performed within 6-12 months after the damage [24].

Table 5. Summary of previously published data

Author	Age	Sex	Time of onset	Vaccine	Treatment	Outcome
Sophie C.	49	Male	13 hours	Pfizer/BioNTech	Steroids	Improvement
Queler [20]	44	Male	18 hours	Moderna	Gabapentin	Improvement
Mahajan [21]	50	Male	1 week	Pfizer/BioNTech	Steroids	Improvement
Crespo Burillo J.A. [28]	38	Male	4 Days	AstraZeneca	Steroids	Improvement
Diaz-Segarra N [29]	35	Women	9 days	Pfizer/BioNTech	Steroids	Improvement
Waheed W [30]	57	Women	1 week	Pfizer/BioNTech	Gabapentin	Improvement
Jason R. Coffman [31]	66	Women	4 weeks	Pfizer/BioNTech	Steroids	Improvement
Our case	78	Male	4 weeks	Pfizer/BioNTech	Steroids	Improvement

4. CONCLUSION

To protect the general population from the SARS-CoV-2 virus infection, the COVID-19 immunization effort is being implemented. There will be an increase in the number of cases of this kind as the vaccination rate continues to rise worldwide. To improve therapeutic outcomes, it is essential to be aware of this association to facilitate timely recognition and management.

Learning Points/Take Home Messages:

- Parsonage-Turner Syndrome (PTS) is a rare condition that is characterized by neurological deficits and neuropathic discomfort.
- PTS is frequently observed due to vaccinations, infections, and mechanical injuries.
- The primary method of diagnosis is clinical, with ancillary support from electrodiagnostic testing (EMG) and imaging (MRI, HRUS).
- Physicians should be prepared to intervene promptly as the number of PTS cases increases, given the robust vaccination programs.
- PTS is typically self-resolving and has a favorable prognosis.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Parsonage MJ, Turner JA. Neuralgic amyotrophy the shoulder-girdle syndrome. The Lancet. 1948.26;251(6513):973-8.
2. Van Alfen N, Van Engelen BG. The clinical spectrum of neuralgic amyotrophy in 246 cases. Brain. 2006 Feb 1;129(2):438-50.
3. RIGAL, BANNEL, FLORENTIN, et al. Parsonage and Turner's neuralgic amyotrophy or shoulder syndrome; A new postvaccinal case. J Med Bord. 1956;133(4):363-364.
4. Amjad MA, Hamid Z, Patel Y, Husain M, Saddique A, Liaqat A, Ochieng P. COVID-19 vaccine-induced Parsonage-Turner syndrome: a case report and literature review. Cureus. 2022 May;14(5).
5. Kuhlenbäumer G, Hannibal MC, Nelis E, et al. Mutations in SEPT9 cause hereditary neuralgic amyotrophy. Nature genetics. 2005;37(10):1044-6.
6. van Alfen N, van Eijk JJ, Ennik T, et al. Incidence of neuralgic amyotrophy (Parsonage Turner syndrome) in a primary care setting-a prospective cohort study. PloS one. 2015.27;10(5):e0128361.
DOI: 10.1371 /journal.pone.0128361.

7. Pessa ME, Verriello L, Valente M, et al. A rare case of pure sensitive Parsonage-Turner syndrome. Neurol Sci. 2019;40(7):1499-501.
8. Lindgren B, Rivers D, Clark J. Bilateral Parsonage-Turner Syndrome After Initial Unilateral Presentation: A Case Report. Cureus. 2019 19;11(12):e6422.
DOI: 10.7759/cureus.6422.
9. Shaikh MF, Baqai TJ, Tahir H. Acute brachial neuritis following influenza vaccination. BMJ Case Rep. 2012. 28;2012:e2012007673.
DOI: 10.1136/bcr-2012-007673.
10. van Eijk JJ, Madden RG, van der Eijk AA, et al. Neuralgic amyotrophy and hepatitis E virus infection. Neurol. 2014.11;82(6):498-503.
11. Van Alfen N. Diagnosing neuralgic amyotrophy: choosing the right test at the right time. Muscle Nerve. 2017.56(6):1020-1.
12. ArÁnyi Z, Csillik A, DéVay K, et al. Ultrasonography in neuralgic amyotrophy: Sensitivity, spectrum of findings, and clinical correlations. Muscl Nerve. 2017.56(6):1054-62.
13. Krishnan KR, Wolfe SW, Feinberg JH, et al. Imaging and treatment of phrenic nerve hourglass-like constrictions in neuralgic amyotrophy. Muscle Nerve. 2020.62(5):81–82.
14. Sneag DB, Rancy SK, Wolfe SW, et al. Brachial plexitis or neuritis? MRI features of lesion distribution in Parsonage–Turner syndrome. Muscle Nerve. 2018.58(3):359-66.
15. Suarez GA, Giannini C, Bosch EP, et al. Immune brachial plexus neuropathy: suggestive evidence for an inflammatory-immune pathogenesis. Neurol. 1996.1;46(2):559-61.
16. Van Alfen N. Clinical and pathophysiological concepts of neuralgic amyotrophy. Nature Reviews Neurolo. 2011.7(6):315-22.
17. Beghi E, Kurland LT, Mulder DW, et al. Brachial plexus neuropathy in the population of Rochester, Minnesota, 1970–1981. Ann Neurol. 1985;18(3): 320-3.
18. Sneag DB, Saltzman EB, Meister DW, et al. MRI bullseye sign: an indicator of peripheral nerve constriction in Parsonage-Turner syndrome. Muscle Nerve. 2017;56(1):99-106.
19. Tsairis P, Dyck PJ, Mulder DW. Natural history of brachial plexus neuropathy: Report on 99 patients. Arch Neurol. 1972.1;27(2):109-17.
20. Queler SC, Towbin AJ, Milani C, et al. Parsonage-Turner syndrome following COVID-19 vaccination: MR neurography. Radiology. 2022; 302(1):84-7.
21. Mahajan S, Zhang F, Mahajan A, et al. Parsonage Turner syndrome after COVID-19 vaccination. Muscle Nerve. 2021;64(1):3–4.
22. Ritchie H, Mathieu E, Rodés-Guirao L, et al. Coronavirus Pandemic (COVID-19). Our World in Data; 2020.
23. Chen RT, Rastogi SC, Mullen JR, et al. The vaccine adverse event reporting system (VAERS). Vaccine. 1994. 1;12(6):542-50.
24. Gstoettner C, Mayer JA, Rassam S, et al. Neuralgic amyotrophy: A paradigm shift in diagnosis and treatment. J Neurol Neurosurg Psychiat. 2020. 1;91(8):879-88.

25. van Alfen N, van Engelen BG, Hughes RA. Treatment for idiopathic and hereditary neuralgic amyotrophy (brachial neuritis). Cochrane Database Syst Rev. 2009. 8;2009(3):CD006976.
DOI: 10.1002/14651858
26. Feinberg JH, Doward DA, Gonsalves A. Cervical radiculopathy vs Parsonage-Turner syndrome: a case report. HSS J. 2007;3(1):106-11.
27. Misamore GW, Lehman DE. Parsonage-Turner syndrome (acute brachial neuritis). J Bone Joint Surg Am. 1996;78(9):1405-8.
28. Crespo Burillo JA, Loriente Martínez C, García Arguedas C, et al. Amyotrophic neuralgia secondary to Vaxzevri (Astra Zeneca) COVID-19 vaccine. Neurologia Engl Ed. 2021;36(7):571-572.
29. Diaz-Segarra N, Edmond A, Gilbert C, et al. Painless idiopathic neuralgic amyotrophy after COVID-19 vaccination: A case report. PM R. 2021;22:10.1002/pmrj.12619.
DOI: 10.1002/pmrj.12619.
30. Waheed W, Carey ME, Tandan SR, et al. Post COVID-19 vaccine small fiber neuropathy. Muscle Nerve. 2021;64(1):1-2.
DOI: 10.1002/mus.27251.
31. Coffman JR, Randolph AC, Somerson JS. Parsonage-Turner Syndrome After SARS-CoV-2 BNT162b2 Vaccine: A Case Report. JBJS Case Connect. 2021. 24;11(3).
DOI: 10.2106

Biography of author(s)

Mohammad Asim Amjad
Pulmonary and Critical Care Medicine, The University of Texas Science Center at Houston, Houston, Texas, USA.

Research and Academic Experience: I am passionate about the research of chest infections and the comprehension of the immunological and pathophysiological components of rare pulmonary diseases.

Research Interest: My research area mainly include Chest Infections, COVID-19 Pandemic, Immunology, and Rare Pulmonary infections.

Zamara Hamid
Internal Medicine, Shifa International Hospital, Islamabad, Pakistan.

Research and Academic Experience: I have a strong enthusiasm for studying infections, and pandemics and understanding the physiological foundations of diseases.

Research Interest: My key research area includes COVID-19 Pandemic and Sepsis.

Yamini Patel
Internal Medicine, The Wright Center for Graduate Medical Educations, Scranton, PA, USA.

Research and Academic Experience: I have many years of research and academic experience.

Research Interest: My area of interest and experience is general medicine, specifically the way different infections interact with the body's physiology and manage the disease's progression. My research also focus on ARDS, Pneumonia, and Viral Infections as my research interest.

Mujtaba Husain
Internal Medicine, The Wright Center for Graduate Medical Educations, Scranton, PA, USA.

Research and Academic Experience: I have many years of research and academic experience.

Research Interest: I have an interest in the field of general medicine, particularly in studying the interplay between different diseases and the physiological processes involved, as well as the management strategies employed throughout the disease. Apart from that, My research area also focuses on Hospital medicine and general medicine.

Ammad Saddique
Internal Medicine, The Wright Center for Graduate Medical Educations, Scranton, PA, USA

Research and Academic Experience: I am fascinated by the interaction of various host factors with epidemiology medicine's physiology and management procedures.

Research Interest: My research area includes Epidemiology and General Medicine.

Adnan Liaqat
Pulmonary and Critical Care Medicine, Mclaren Health/Michigan State University, Lansing, MI, USA.

Research and Academic Experience: I am interested in studying acute respiratory distress syndrome (ARDS) and other pulmonary disorders, particularly their pathophysiology aspects.

Research Interest: My research domain involves ARDS, Pneumonia, and Atypical Infections.

Pius Ochieng
Pulmonary and Critical Care Medicine, Geisinger Community Medical Center, Scranton, PA, USA.

Research Interest: My research areas include Pulmonary hypertension, and Pneumonia.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Cureus, 14(5): e25493, 2022. DOI: 10.7759/cureus.25493

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1189

Chapter 8
Print ISBN: 978-81-976653-0-1, eBook ISBN: 978-81-976653-1-8

Predicting Prognosis of Acute Pancreatitis Patient in a Tertiary Centre with Help of BISAP Scoring

Kanwar Singh Goel [a++*], Nikhil Goel [b#] and Sapna Singla [c†]

DOI: https://doi.org/10.9734/bpi/dhrni/v1/1247

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1247

ABSTRACT

Introduction: Acute pancreatitis is an acute inflammation of the prior normal pancreas. Gallstones are its leading cause, followed by alcohol; other etiological factors are hyperlipidemia, hereditary, hypercalcemia and post ERCP, etc. Its pathogenesis involves the activation of intrapancreatic digestive enzymes and the injury of acinar cells. Many scoring systems are available to assess the severity of acute pancreatitis, e.g., Ranson's criteria, Glasgow score index, APACHE II and CTSI, but they have important limitations. BISAP score is a valuable tool in predicting severe Acute Pancreatitis in the early hours. BISAP score appears cheap, quick, and simple and hence, we conducted this study.
Material and Methods: This prospective observational study was carried out in 83 patients at SGT Medical College, Gurugram, India from September 2018 to March 2021. Patients with an established diagnosis of acute pancreatitis as per the revised Atlanta classification and definition by the International Census 2012 were included in the study. BISAP scores were calculated from laboratory values and radiological findings.
Results: In our patients with BISAP scores of 0, 1 and 2, there was no organ failure or mortality. At a score of 3, there was 1 (07.1%) organ failure and 1 (07.1%) mortality. At a score of 4, 4 (80.0%) patients had organ failure and 1(20.0%) patient died. We observed that the higher the BISAP score, the higher the percentage of severity, necrosis, organ failure, mortality and hospital stay.

[a] Department of General Surgery, SGT Medical College, SGT University, Budhera, Gurugram, Haryana, India.
[b] Department of Psychiatry, Shaheed Hasan Khan Mewati Government Medical College, Nuh, India.
[c] Department of Pathology, Shaheed Hasan Khan Mewati Government Medical College, Nuh, India.
[++] Professor & Head;
[#] Associate Professor and HOD;
[†] Assistant Professor;
**Corresponding author: E-mail: dr.kanwarsinghgoel@rediffmail.com;*

Our study revealed that with the cutoff value set at 3, the BISAP score has 39.6% sensitivity, 92.8% specificity, 60.3% PPV and 84.7% NPV.
Conclusion: Our study recommends that at the time of admission, if the BISAP score is low, our worry is less, if the BISAP score is high, we should counsel the patient and attendants about possible severity, necrosis, organ failure and mortality in acute pancreatitis. Patients should be meticulously managed. The present study concludes the increased accuracy of the BISAP score for risk stratification.

Keywords: Acute pancreatitis; BISAP score; organ failure; mortality.

1. INTRODUCTION

Acute pancreatitis is an acute inflammation of the prior normal pancreas. The incidence of acute pancreatitis is estimated at 110 to 140 per 100,000 population, with an estimated more than 300,000 US emergency department visits per year. Acute pancreatitis is a disease of the exocrine pancreas that causes severe abdominal pain and multiple organ dysfunction that may lead to pancreatic necrosis and persistent organ failure, with a mortality of 1–5% [1]. Gallstones are its leading cause (30-60%), followed by alcohol (15-30%), other etiological factors are hyperlipidemia, hereditary, hypercalcemia and post ERCP etc. [2]. The rate of occurrence of each etiology of acute pancreatitis varies across geographic regions and socioeconomic strata [3,4].

Its pathogenesis involves three phases. The first phase is characterized by the activation of intrapancreatic digestive enzymes and the injury of acinar cells. In the second phase, there is activation, chemo-attraction and sequestration of leukocytes and macrophages in the pancreas causing increased intrapancreatic inflammatory reaction. The third phase is due to the effects of activated proteolytic enzymes and cytokines released by the inflamed pancreas, on various organs [5]. As a result of the cascade of local and distant effects, systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), as well as multiorgan failure may occur.

Acute pancreatitis is classified into three forms based on the severity. Mild acute pancreatitis, which is characterized by the absence of organ failure and local or systemic complications; Moderately severe acute pancreatitis, which is characterized by transient organ failure (resolves within 48 hours and without persistent organ failure >48 hours) and/or local or systemic complications; and Severe acute pancreatitis, which is characterized by persistent organ failure that may involve one or multiple organs [6]. Patients present with mild to severe steady and boring pain in the epigastrium and periumbilical region. Pain may radiate to the flanks, back, chest and lower abdomen. Nausea, vomiting, and abdominal distension frequently accompany [7]. Physical examination reveals an anxious patient with low-grade fever, and tachycardia, with or without hypotension. Jaundice is infrequent. Abdominal examination may reveal a tender, guarded abdomen. Cullen's sign and Turner's sign may be present in severe cases [8]. Pancreatitis is broadly classified into mild and severe varieties.

Mild pancreatitis is usually self-limiting. Severe acute pancreatitis has a high mortality (about 20%-30% as compared to overall mortality of 2-5% in acute pancreatitis) [9]. Since there is high mortality in severe acute pancreatitis hence, we should determine the severity in the emergency ward itself so that patient triage can be done. Patients with mild disease can be treated in the general ward and those with severe diseases can be managed by more aggressive treatment in specialized center with good intensive care facilities, anesthesia, endoscopic lab and surgical facilities. Therefore, arose the necessity of prognostic factors that allow the clinician to accurately predict the severity of disease. Nowadays many scoring systems are available to assess the severity of acute pancreatitis, e.g., Ranson's criteria [10], acute physiology and chronic health evaluation (APACHE II) [11,12] and computed tomography severity index (CTSI) [13]. These scoring methods of risk stratification in acute pancreatitis have important limitations, especially in developing countries like ours. Most hospitals cannot afford the requirements of Ranson's and Modified Glasgow Score Index. In addition, both these scoring systems take 48 hours for complete evaluation. APACHE II determines the disease severity on the day of admission but it is very complex [14,15]. CTSI is based on the use of the CECT abdomen. CECT is not available in all hospitals in our country. Moreover, it is not used as a basis of clinical decision-making. Thus, there is a need to find a scoring system that can prognosticate the disease at the earliest, which is cheap, quick, simple, accurate and easily reproducible and can be used comfortably in our country. In 2008, Wu et al developed a clinical scoring system using classification and regression tree analysis for prediction of in-hospital mortality of acute pancreatitis [8]. This is the Bedside Index for Severity in Acute Pancreatitis (BISAP) score. On this score, several studies have been done in Western countries. In India, only a few studies have been done. We conducted this prospective observational study, to evaluate the BISAP score in predicting the outcome of acute pancreatitis, in our part of the country.

2. MATERIALS AND METHODS

Study Design: Prospective observational study.

Study Site: SGT Medical College, SGT University, Budhera, Gurugram, Haryana, India.

Study Period: September 2018 to March 2021.

Study Population: 83 consecutive patients who were admitted with a diagnosis of acute pancreatitis in various surgery wards of SGT Medical College were considered for the study.

Inclusion Criteria: Patients with an established diagnosis of acute pancreatitis as per the revised Atlanta classification and definition by International Census 2012, were included in the study.

Exclusion Criteria: Patients with chronic pancreatitis were excluded from surgery [8].

2.1 Operational Definitions

Acute pancreatitis- as per revised Atlanta classification and definition by International Census 2012, is defined as patients having two of the following three features a) characteristic abdomen pain, b) elevation of pancreatic enzymes more than three times the normal values, c) characteristic findings in CECT i.e., oedema of the pancreas, altered fat and fascial planes, fluid collections, necrosis (non-enhancement area more than 30% or 3 cm) [16,17].

Severity grading: includes the following. Mild acute pancreatitis (MAP)- is defined as when there is no organ failure and no local or systemic complications. Severe acute pancreatitis (SAP)- is defined as when there are local or systemic complications with or without persistent organ failure. Transient organ failure- is the organ failure that resolves in 48 hours. Persistent organ failure- when organ failure persists for more than 48 hours. It may be single or multiple organ failure. Organ failure- three organ systems should be assessed to define organ failure. a) Pulmonary insufficiency- when arterial PO_2 is less than 60 mm Hg in room air or there is a need for a ventilator, b) renal failure- serum creatinine level more than 2 mg % after rehydration or haemodialysis, c) shock- systolic blood pressure less than 90 mm Hg. As per the Modified Marshall scoring system, a score of 2 or more for one of these three organ systems, suggests organ failure [8].

BISAP score- incorporates five clinical and lab parameters obtained within the first 24 hours of admission. a) Blood urea nitrogen (BUN) >25 mg%, b) impaired mental status, c) Glasgow coma score < 15, d) Age >50 years, e) Systemic inflammatory response syndrome (SIRS) – when two or more of the followings are present i.e., i core body temperature <36°C or >38°C, ii heart rate >90/minute, iii respiratory rate >20/minute, iv WBC count <4000 cells/mm^3 or > 12000 cells/mm^3. Each score is given 1 point. A score of zero was awarded in case of absence of any of these factors. The total BISAP score was calculated within 24 hours. Various possible outcomes of the study were severity, necrosis, organ failure and death.

2.2 Procedure and Data Collection

Patients presenting with features of acute pancreatitis were admitted, a detailed history was taken and thorough local and systemic examinations were made. Patients were investigated for complete blood count, blood glucose level, kidney function tests, liver function tests, serum calcium, serum amylase, C-reactive protein, plain radiograph of the abdomen and chest, and an ultrasound scan of the abdomen [8]. If ultrasound findings were doubtful or diagnosis could not be established, contrast-enhanced computed tomography (CECT) abdomen was done. We did not do CECT in all the patients to minimize the expenditures. BISAP scores were calculated from laboratory values and radiological findings. If the BISAP score was low, patients were managed in the general ward, if the score was higher, patients were admitted in intensive care units and managed.

2.3 Analysis Plan

The data were collected properly and entries were made. Numeric data are presented as mean ± SD. Simple mathematical expressions like percentages were also used. Statistical analyses were performed using the Statistical Package for Social Science (SPSS) software, the latest version. Sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were calculated.

Quality Assurance: This was ensured at each and every step. Patients were enrolled in an unbiased fashion.

Ethical Considerations: The institutional ethics committee's approval for research on human subjects was taken. Throughout the study, strict ethical norms were maintained. Written informed consent was taken from patients in their local language (mother tongue) [8].

3. RESULTS

The study was carried out on 83 patients. In 79 patients, diagnosis could be established as per the definition of acute pancreatitis. In 4 patients help of CECT was taken to establish the diagnosis. 18 patients were 60 years or more than 60 years old and 65 patients were less than 60 years of age. The median age of patients was 55.8 ± 20.7 years in severe acute pancreatitis and 52.8 ± 16.3 in mild acute pancreatitis.

Table 1. Age distribution

Age in years	Numbers of patients	MAP*	SAP**	Significance (p value)
Less than 20	1 (1.2%)	1 (100%)	0	
20-29	9 (10.8%)	8 (88.9%)	1 (11.1%)	
30-39	20 (24.1%)	17 (85%)	3 (15.0%)	
40-49	23 (27.7%)	20 (87.0%)	3 (13.0%)	0.0783
50-59	12 (14.4%)	10 (83.3%)	2 (16.7%)	
60 or more	18 (21.7%)	10 (55.6%)	8 (44.4%)	

Table 2. Characteristics of patients (n=83)

Characteristics		SAP	MAP	P
Sex(number)	Male	9 (52.9%)	37 (66.0%)	0.287
	Female	8 (47.1%)	29 (34.0%)	
Etiology (number)	Gall Stone	10 (58.8%)	43 (65.2%)	
	Alcohol	4 (23.5%)	13 (19.7%)	0.009
	Post ERCP	1 (6.0%)	4 (6.0%)	
	Idiopathic	2 (11.7%)	6 (9.1%)	

We have observed that the percentage of severity, necrosis, organ failure, mortality, and hospital stay were higher in severe acute pancreatitis as compared to mild acute pancreatitis (Table 4) [8]. The present study reveals that as the BISAP score increases, the severity, necrosis, organ failure and mortality also increase.

Table 3. Distributions of cases according to BISAP point scores

BISAP score		Numbers of cases
BUN*	≥ 25 mg%	14 (16.8%)
	< 25 mg%	69 (83.2%)
Impaired mental status	Present	1 (01.2%)
	Absent	82 (98.8%)
SIRS**	Present	34 (40.9%)
	Absent	49 (59.1%)
Age	≥ 60 years	18 (21.7%)
	< 60 years	65 (78.3%)
Pleural effusion	Present	24 (28.9%)
	Absent	59 (71.1%)

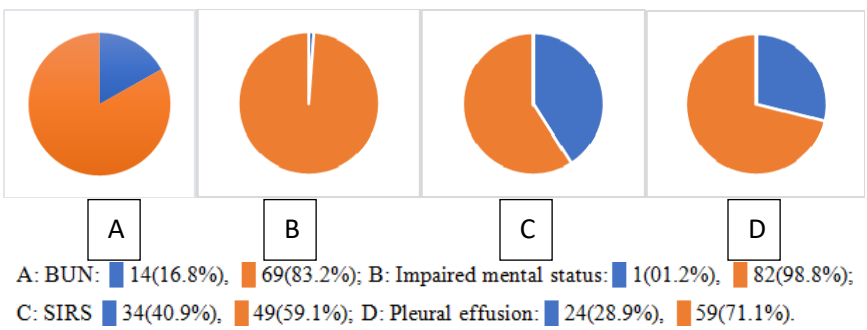


Fig. 1. Distribution of cases according to BISAP point scores

Table 4. Clinical Characteristics and Outcomes of Patients (n=83)

Characteristics		Data
Severity	SAP	17 (20.5%)
	MAP	66 (79.5%)
Necrosis	Present	22(26.5%)
	Absent	61(73.5%)
Organ failure	Present	05(06.0%)
	Absent	78(94.0%)
Hospital stay (days)	SAP	11.02±5.64
	MAP	6.78±3.29
Mortality		2 out of 17 patients of SAP (11.8%)

In our patients with BISAP scores of 0,1 and 2, there was no organ failure or mortality. At a score of 3, there was 1 (07.1%) organ failure and 1 (07.1%) mortality. At a score of 4, 4 (80.0%) patients had organ failure and 1(20.0%) patient died. We had no patient with a BISAPscore of 5 (Table 5).

Table 5. BISAP point scores and distribution of severity, necrosis, organ failure and mortality

BISAP Score	Severity (Number, %)	Necrosis (Number, %)	Organ failure (Number, %)	Mortality (Number, %)	Total (Number, %)
0	0	3(9.1)	0	0	33(39.7)
1	1(04.7)	4(19.0)	0	0	21(25.3)
2	3(30.0)	4(40.0)	0	0	10(12.0)
3	8(57.1)	7(50.0)	1(07.1)	1(07.1)	14(16.8)
4	5(100)	4(80.0)	4(80.0)	1(20.0)	5(06)
5	0	0	0	0	0(00)
Total	17	22	5	2	83 (100)

Our statistical analysis revealed that with the cutoff value set at 3, the BISAP score has 39.6 % sensitivity, 92.8 % specificity, 60.3% PPV and 84.7% NPV (Table 6).

Table 6. Sensitivity, specificity, PPV and NPV of BISAP scoring system in predicting SAP

Sensitivity	39.6%
Specificity	92.8%
PPV	60.3%
NPV	84.7%

4. DISCUSSION

In our study, we evaluated the BISAP score in predicting the outcome of acute pancreatitis. There are many existing prognostic scoring systems. But these have many problems, especially for hospitals in our country which cannot afford to fulfill all the criteria included in these scores. Ranson's and Glasgow's scores need 48 hours for calculation, and these scores require data that is not easily available in small centers [18,19,20,21]. APACHE II requires many parameters but some of these parameters are not useful. It was basically designed as an intensive care unit instrument [16] The chronic health profile portion of this score requires knowledge of patient history and medication details which may not be available if the patient is unconscious, intubated, or transferred from outside the hospital with few medical records. It is also difficult to remember this score [22,23,8]. These require data collected at the time of admission and then at 48 hours. CTSI also has limitations as told in the introduction part. So, there is a need to find a scoring system which can prognosticate the diseases at the earliest which is easily reproducible, cheap and can be used at every step of health care, especially in a country like ours. The BISAP scoring system is

probably comfortable in all these respects. Both the BISAP and APACHE II scores incorporate systemic inflammatory response syndrome, age and Glasgow coma score [24] BISAP score has many advantages. Here, data can be easily obtained at the time of admission. It also warns us of increased risk to patients with high BISAP scores [9,25]. Acute pancreatitis affects all ages and most of the cases are in the age group 21 to 50 years, which is the age where a person earns the bread and butter in the family. Thus, the disease affects a person in other ways besides the illness itself. Many patients were more than 40 years of age. This is explained by the fact that biliary tract diseases are an important cause of pancreatitis and have a higher prevalence in this part of the country. We had 17 patients with severe acute pancreatitis. Many of these were more than 60 years old. Thus, age is an important parameter. Raised BUN is an independent predictor of severe pancreatitis. There may be several mechanisms for this. Initial BUN values may reflect the volume depletion and pre-renal azotemia. A persistent elevation may reflect a failure to adequate volume replacement [8]. We had raised BUN in 14 (82.3%) out of 17 (100%) patients with severe pancreatitis. There was 1(01.2%) patient of impaired mental status. This may be due to our small sample size and further that mental impairment in acute pancreatitis is uncommon. SIRS is an important factor in determining the outcome of the case. In our study, all the patients with severe acute pancreatitis had positive SIRS. In addition, some patients from mild disease also had positive SIRS. We had 17 patients with severe acute pancreatitis. The presence of pleural effusion should make us more vigilant and aggressive in managing patients (Table 3). In our study, most of the patients suffering from severe acute pancreatitis had pleural effusion. We have found in our study that patients with a BISAP score ≥3 carry a higher risk of severity, necrosis, organ failure and mortality, than BISAP score of <3 (Table 4). We had 1 organ failure and 1 mortality in patients with a BISAP score of 3. In patients with a BISAP score of 4, we had 4 organ failures (1 patient had shock, 1 had pulmonary insufficiency and 3 patients had renal failure (Table 5). Our study reveals that the cut-off value set at 3, BISAP score is having 39.6% sensitivity, 92.8% specificity, 60.3% PPV and 84.7% NPV (Table 6) [8]. A study by Papachristou et al. [26] reported that with the same cutoff value, the BISAP score had a sensitivity of 37.5%, a specificity of 92.4%, a PPV of 57.7% and an NPV of 84.3% in predicting severe acute pancreatitis. A study by Sumitra Hagjer, and Nitesh Kumar [27] showed that there was an increasing trend in the percentage of severity, organ failure, necrosis and mortality with increasing BISAP scores. A study by Akhtar Mohammad [28] demonstrated that BISAP has the advantages of simplicity and speed over traditional scoring systems and performs similarly to other scoring systems in predicting SAP and the prognoses. Thus, our results are comparable with all these studies.

5. CONCLUSION

Our study recommends that at the time of admission, if the BISAP score is low, our worry is less, if the BISAP score is high, we should counsel the patient and attendants about possible severity, necrosis, organ failure and mortality in acute pancreatitis. We should be meticulous in managing such patients. We conclude that the BISAP score is a reliable means of predicting the severity, necrosis,

organ failure and mortality in patients with acute pancreatitis. There is an increasing trend in these outcomes with increasing BISAP scores. The present study concludes the increased accuracy of the BISAP score for risk stratification in our patients [8].

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Mederos MA, Reber HA, Girgis MD. Acute pancreatitis: A review. Jama. 2021 Jan 26;325(4):382-90.
2. Kasper Dennis L, Hauser Stephen L, Jameson J Larry, Fauci Anthony S, Longo Dan L, Loscalzo Joseph. Harrison's principles of internal medicine. 19th Ed. New York: McGraw Hill Education; 2015.
3. Lee PJ, Papachristou GI. New insights into acute pancreatitis. Nature reviews Gastroenterology & hepatology. 2019 Aug;16(8):479-96.
4. Gliem N, Ammer-Herrmenau C, Ellenrieder V, Neesse A. Management of severe acute pancreatitis: An update. Digestion. 2021 Jul 18;102(4):503-7.
5. Cochior D, Constantinoisu S. Factors involved in the pathogenesis of acute pancreatitis. Chirurgia (Bucur). 2010;105(4):445-53.
6. Chanda A. Severe acute pancreatitis and its management. InIntensive Care; 2017 Jul 12. Intech Open.
7. Gao YJ, Li YQ, Wang Q, Li SL, Li GQ, Ma J, et al. Analysis of clinical features of acute pancreatitis in Shandong Province, China. J Gastroenterol Hepatol. 2007;22(3):340-44.
8. Goel S, Goel N, Goel KS. Evaluation of BISAP Score in Predicting Outcome of Acute pancreatitis in a tertiary centre. International Journal of Health and Clinical Research. 2021;4(14):68-72.
9. Vikesh K Singh, et al. A prospective evaluation of the bedside index for severity in acute pancreatitis score in assessing mortality and intermediate markers of severity in acute pancreatitis. Am. J. Gastroenterol. 2009;104(4):966-971.
10. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet. 1974;139(1):69-81.
11. McMahon MJ et al. APACHE-II score for assessment and monitoring of acute pancreatitis. Lancet. 1989;2(8656):201-5.
12. Johnson CD, Toh SK, Campbell MJ. Combination of APACHE-II score and an obesity score (APACHE-O) for the prediction of severe acute pancreatitis. Pancreatology. 2004;4(1):1-6.
13. Pezzilli R, et al. Practical guidelines for acute pancreatitis. Pancreatology. 2010;10(5):523-535.

14. Yeung YP, Lam BY, Yip AW. APACHE system is better than Ranson system in the prediction of severity of acute pancreatitis. Hepatobiliary Pancreat Dis Int. 2006;5(2):294-299.
15. Larvin M, McMahon MJ. APACHE II score for assessment and monitoring of acute pancreatitis. Lancet. 1989;2(8656):201-205.
16. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: A large population-based study. Gut. 2008;57(12):1698-1703.
17. SriramBhat. SRB's Manual of Surgery. 5th edition. New Delhi: Jaypee Brothers Medical Publishers; 2016.
18. Park, Ji Young, et al. Bedside index for severity in acute pancreatitis: comparison with other scoring systems in predicting severity and organ failure. Hepatobiliarypancreat. Dis, Int. 2013;12(6):645-650.
19. Peter A. Banks, Martin L, Freeman. Practice guidelines in acute pancreatitis. Am. J, Gastroenterol. 2006;101(10):2379.
20. J.H.C. Ranson, prognostic signs and the role of operative management in acute pancreatitis. Surg. Gynecol. Obstet. 1974;139:69-81.
21. John HC, Ranson, Berard S, Pasternack. Statistical methods for quantifying the severity of clinical acute pancreatitis. J. Surg. Res. 1977;22(2):79-91.
22. Young-Seok Cho et al. Usefulness of the Bedside index for severity in acute pancreatitis in the early prediction of severity and mortality in acute pancreatitis. Pancreas. 2013;42(3):483-487.
23. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med. 1985 Oct;13(10): 818-29.
PMID: 3928249.
24. Singh VK, Wu BU, Bollen TL, Repas K, Maurer R, Johannes RS, et al. A prosoective evaluation of the bedside index for severity in acute pancreatitis score in assessing mortality and intermediate markers of severity in acute pancreatitis. AM J Gastrroenterol. 2009;104(4): 966-71.
25. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: A large population-based study. Gut. 2008 Dec;57(12):1698-703.
DOI: 10.1136/gut.2008.152702
Epub 2008 Jun 2. PMID: 18519429.
26. Papachristou GI, Muddana V, Yadav D, O'Connell M, Sanders MK, Slivka A, Whitcomb DC. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. Am J Gastroenterol. 2010 Feb;105(2):435-41; quiz 442.
DOI: 10.1038/ajg.2009.622
Epub 2009 Oct 27. PMID: 19861954.
27. Hagjer S, Kumar N. Evaluation of the BISAP scoring system in prognostication of acute pancreatitis – A prospective observational study; 2018.
Available:https://doi.org/10.1016/j.ijsu.2018.04.026
28. Akhtar, Mohammad. Evaluation of the BISAP Score in Predicting Severity and Prognosis of Acute Pancreatitis in Indian Patients. 2023;55-61.

Biography of author(s)

Dr. Kanwar Singh Goel (Professor & Head), M.S. (General Surgery)
Department of General Surgery, SGT Medical College, SGT University, Budhera, Gurugram, Haryana, India.

Research and Academic Experience: I have 14 years of post-M.S. Surgery, teaching experience in medical colleges. Presently, I have been working as a professor and head of the Department of Surgery, for the last 2 years. I am a devoted teacher for undergraduate (M.B.B.S.) and post-graduate (M.S.) students.

Research Specialization: My research domain includes extensive research specialization, covering many surgical problems, e.g. breast, thyroid, appendix, pancreas, anorectal problems, abdominal tuberculosis, and urology problems.

Number of Published papers: About 22 papers were published in various national and international journals. About 30 papers were presented at various national and international conferences. Among them, two are award-winning papers.

Special Award: I have received the Golden Research Award for best research.

Any other remarkable point(s): I am a reviewer of many national and international journals.

Dr. Nikhil Goel (Associate Professor and HOD)
Department of Psychiatry, Shaheed Hasan Khan Mewati Government Medical College, Nuh, India.

Research and Academic experience: He has more than 10 years of experience in Psychiatry, along with that he pursued a Certificate Course in Child and Adolescent Psychiatry. He is actively involved in UG and PG teaching processes.

Research Specialization: His research domain involves many areas such as marriage and psychiatry, suicide and cholesterol levels, substance use, and women's mental health.

Number of Published papers: He has published 20 papers in indexed national and international journals.

Special Award: He is the recipient of the 2nd award for the Best Research Paper on COVID-19 Pandemic Social Impact by Govt of Haryana, India.

Dr. Sapna Singla (Assistant Professor)
Department of Pathology, Shaheed Hasan Khan Mewati Government Medical College, Nuh, India.

Research and Academic experience: She has 10 years of experience in pathology.

Research Specialization: Her research domain involves histopathology and oncopathology.

Number of Published papers: She has published 25 papers in several indexed national and international journals.

Special Award: She has been awarded 1st prize at the Dermapath Conference for Paper Presentation. Moreover, she is the recipient of the 2nd Prize in a Paper titled: Ultrasound-guided FNAC in space-occupying lesions of Liver held at Medanta Hospital, Gurugram, India.

Any other remarkable point(s): She has been actively involved in UG and PG teaching.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
International Journal of Health and Clinical Research, 4(14): 68-72, 2021.
Available:https://ijhcr.com/index.php/ijhcr/article/view/2261

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1247

Chapter 9
Print ISBN: 978-81-976653-0-1, eBook ISBN: 978-81-976653-1-8

Perceptions of Risk Factors and Complications of Obesity in Female Medical Students of South India: A Cross-Sectional Study

Pravin N Yerpude [a++*] and Keerti S Jogdand [a#]

DOI: https://doi.org/10.9734/bpi/dhrni/v1/1378

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1378

ABSTRACT

Aim: The present study aimed to find out the extent of the problem of obesity and to assess the subjects' awareness of risk factors and complications of obesity.
Introduction: The World Health Organisation has described obesity as one of the most neglected public health issues. Initially, obesity was only a problem in high-income countries; however, at present, it is rising in middle and low-income countries as well, rapidly in India. Globally, non-communicable diseases are increasingly recognized as a major cause of morbidity and mortality. The countries of the Southeast Asia region are facing a double burden, with a heavy load of infectious diseases and an increasing burden due to non-communicable diseases. The growing prevalence of non-communicable diseases, especially in emerging nations like India, poses a challenge to the already overburdened healthcare system. Non-communicable diseases include a variety of illnesses, with obesity being a more frequent cause.
Materials and Methods: The present cross-sectional study was carried out in November 2012. The study was conducted among all 1st and 2nd year female MBBS students of Katuri Medical College, Guntur (Andhra Pradesh). Height and weight were measured using the standard procedures suggested by Jelliffe. Body Mass Index was computed using the formula [weight in (kg) / height (m2)].
Results: Using the BMI cut-off points, the findings revealed that 23.30 % of study subjects were overweight and 12.50 % of study subjects were obese. When the

[a] Department of Community Medicine, Chhindwara Institute of Medical Sciences, Chhindwara (M.P.)-480001, India.
[++] Professor and HOD;
[#] Associate Professor;
**Corresponding author: E-mail: drpravinyerpude@gmail.com;*

girls were asked about factors contributing to obesity, an overwhelming majority (85.80%) of the subjects attributed diet to obesity. As far as psychosocial problems are concerned, nearly 59.66 of the subjects mentioned low self-esteem as a complication related to obesity. Obesity is known to increase the risk of various diseases and awareness of them is the first step towards taking steps to prevent this. While a high level of awareness is present among medical students regarding major complications of obesity but for other complications, they should also get health education.

Conclusion: The higher prevalence of overweight and obesity in this young age range necessitates immediate attention to prevention and control. Obesity has been linked to an increased risk of a variety of ailments, and becoming aware of this is the first step toward taking preventative measures. While medical students exhibit a high level of awareness regarding major complications of obesity, they should also receive health education regarding other complications. This study is significant for the scientific community due to its focus on perceptions of obesity among female medical students in South India. It provides crucial insights into the prevalence of overweight and obesity, as well as awareness of associated risks among future healthcare professionals.

Keywords: Body mass index; obesity; medical students.

1. INTRODUCTION

Obesity is one of the major lifestyle disorders in India and its incidence has rapidly increased during recent decades. Medical students are more prone to obesity, due to their sedentary lifestyle, lack of exercise, disordered eating habits due to lack of leisure time, increased stress, and vast topics to learn. Thus, they are prone to overweight/obesity-related complications such as hypertension, dyslipidemia, and impaired glucose tolerance [1]. Globally, non-communicable diseases (NCDs) are increasingly recognized as a major cause of morbidity and mortality. The countries of the Southeast Asia region are facing a double burden, with a heavy load of infectious diseases and an increasing burden due to non-communicable diseases [2]. Understanding the physical environment is vital in determining the risk of obesity. Environmental factors include food marketing and advertising, knowledge regarding exercise and nutrition, availability of resources, local walkability and crime, etc., making the role of the environment multifaceted and complex [3]. The increasing burden of non-communicable diseases, particularly in developing countries including India, threatens to overwhelm already stretched health services.

Several diseases come under the umbrella of non-communicable diseases and the more common cause is obesity [4,5,6].

Obesity is perhaps the most prevalent form of malnutrition in developed countries. There has been an increased awareness of the problem in recent years [6]. It has been estimated to affect 20-40% of adults and 10-20% of children and adolescents in developed countries. Physical inactivity may cause

obesity, which in turn restricts activity. This is a vicious circle. It is the reduced energy output that is probably more important in the etiology of obesity [6].

In a recent study conducted in the United States, it was found that the prevalence of obesity is higher among women than among men [7]. In India also some North Indian studies showed the same results [8,6]. Given the fact that an increased risk of cardiovascular disease is associated with obesity, it is essential to know the prevalence of overweight and obesity in populations [6]. It is also necessary to find out how far the population is aware of the causes and consequences of obesity. The aim of this study is to find out the extent of the problem of obesity and to assess the subjects' awareness of risk factors and complications of obesity.

2. MATERIALS AND METHODS

The present cross-sectional study was carried out in November 2012. The study was conducted among all 1st and 2nd-year female MBBS students of Katuri Medical College, Guntur (Andhra Pradesh). Before the start of the study, clearance was taken from the College Ethical Committee [6]. Each student was interviewed personally to collect the required information on a pretested schedule and appropriate privacy was provided to take their anthropometric measurements [6]. Height and weight were measured using the standard procedures suggested by Jelliffe [9]. Body Mass Index was computed using the formula [weight in (kg) / height (m2)]. WHO grading for body mass index (BMI) was used for the determination of actual weight status as underweight (BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI≥ 25) & obesity (BMI ≥30). The data were analyzed using SPSS version 12 [6].

3. RESULTS

In our study, there are a total of 176 female students who participated in the study. The maximum number of students was in the age group of 18-20 years i.e. 114 (64.77%) followed by 56(31.82%) students in the age group of 21 -22 years. A few students 6 (3.41%) were above 22 years of age [6].

Using the BMI cut-off points (as shown in Table 1), the findings revealed that 23.30 % of study subjects were overweight and 12.50 % of study subjects were obese.

Table 1. Distribution of study subjects according to B.M.I. [6]

Classification	BMI cut off points(kg/m^2)	No of subjects	Percentage
Underweight and normal	< 25	113	64.20
Overweight	≥ 25	41	23.30
Obese	≥30	22	12.50
Total		176	100

Table 2. Attributing factors responsible for obesity as per students' opinion

Factors	Underweight and normal (n=113)	Overweight & obese (n=63)	Total (n=176)
Dietary	94(83.19%)	57(90.48%)	151(85.80%)
Sedentary life style	71(62.83%)	43(68.25%)	114(64.77%)
Hereditary	18(15.93%)	21(33.33%)	39(22.16%)
Hormonal disorder	8(7.08%)	11(17.46%)	19(10.80%)

Table 3. Perception of study subjects regarding obesity related complications [6]

Complications	Underweight & normal (n=113)	Overweight & obese (n=63)	Total (n=176)
Psychosocial problems			
Low self-esteem	64(56.64%)	41(65.08%)	105(59.66%)
Appearance	31(27.43%)	17(26.98%)	48(27.27%)
Social interaction	27(23.89%)	15(23.81%)	42(23.86%)
Marriage problems	24(21.24%)	8(12.70%)	32(18.18%)
Physical problems			
Cardiovascular disorder			
Heart disease	73(64.60%)	42(66.67%)	115(65.34%)
Rise in blood pressure	66(58.41%)	39(61.90%)	105(59.66%)
Diabetes mellitus	64(56.64%)	37(58.73%)	101(57.39%)
Locomotor Problems			
Walking trouble due to joint problems/Lack of easy motion	23(20.35%)	18(28.57%)	41(23.30%)
Difficulty in accomplishing task/Posture related problems	21(18.58%)	16(25.40%)	37(21.02%)
Others			
Sleeping trouble	18(15.93%)	15(23.81%)	33(18.75%)
Easy fatigue	10(8.85%)	11(17.46%)	21(11.935)

When the girls were asked about factors contributing to obesity, an overwhelming majority (85.80%) of the subjects attributed diet to obesity. An attempt was further made to analyze the opinions of respondents according to their BMI weight category status; it revealed almost similar responses among the subjects irrespective of their BMI status (Table 2) [6].

As far as psychosocial problems are concerned, nearly 59.66 of the subjects mentioned low self-esteem as a complication related to obesity (Table 3). Regarding physical health, the common complications perceived by the subjects were heart disease (65.34%), a rise in blood pressure (59.66%), and diabetes mellitus (57.39%). As far as locomotor problems were concerned, they were perceived by 44.32% of subjects as a complication of obesity [6].

4. DISCUSSION

In the present study, 23.30 % of study subjects were overweight and 12.50 % of study subjects were obese. A study on “Body Image Perception and Attempts to Change Weight among Female Medical Students at Mangalore” by Priya et al. [10] showed that 25(17%) subjects were undernourished while 111(75.5%) and 11(7.5%) were normally nourished and overweight respectively [6]. The findings of a study by Augustine and Poojara [11] on urban college-going girls of Ernakulam also showed a higher prevalence of overweight and obesity of 24% & 10.5% respectively [6].

In our study, we found that the 18-20 years age group had more prevalence of overweight/obesity. The study conducted by Augustine & Poojara [11] among urban college-going girls of Ernakulam has reported the prevalence of obesity higher among the 18-year age group than beyond that [6].

The study conducted by V. Sekar et al. [12] among women in Coimbatore showed quite a lower level of awareness (69.6%) as compared to our study (85.80%) regarding diet as a cause of obesity. This difference indicates the degree of unawareness of subjects in their study as the present study was conducted only in college [6]. They also reported that a large proportion of the overweight women failed to mention lack of exercise (26%) as contributing to obesity which is less as compared to our study (64.77%).

Sung RY et al. [13] reported more overweight than normal-weight children perceive themselves to have more body fat, and lower physical competence and self-esteem [6]. Our study has reported a relatively lower level of awareness than the study conducted by V. Sekar et al. [12]. among women in Coimbatore who pointed out that 71.3% of urban women were aware of heart attack as a complication of obesity as compared to our study (65.34%), 64.4% vs 59.66% for hypertension, 62.6% vs 57.39 % for diabetes and 60.5% vs 23.30% for arthritis [6]. Also showed in their study that overweight women were more aware than those with normal weight subjects for the complications. This can be due to the fact that their study has been conducted among women for more than 20 years,

and their subjects might be facing such complications among themselves or their peer groups [6].

5. CONCLUSION

The higher prevalence of overweight and obesity in this early age group calls for the prevention and control of this problem with prime attention. Obesity is known to increase the risk of various diseases and awareness of them is the first step towards taking steps to prevent this [6]. While a high level of awareness is present among medical students regarding major complications of obesity but for other complications, they should also get health education.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of manuscripts.

ACKNOWLEDGEMENTS

We would like to acknowledge the study participants for their cooperation.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Thomas E, Geethadevi M. Prevalence and determinants of overweight and obesity among medical students. National Journal of Physiology, Pharmacy and Pharmacology. 2020;10(1):42-8.
2. World health Organization. Non communicable diseases in south East Asia region. New Delhi: Regional Office for South East Asia, India; 2002;78-83.
3. Barua S, Saikia N. Perception, environmental determinants, and health complications of excess weight in India: a mixed methods approach. Scientific Reports. 2023 Apr 11;13(1):5868.
4. Reilly JJ, Dorosty AR. Epidemic of obesity in UK children. Lancet 1999;354:1874-5.
5. Keil U, Kuulasmaa K. WHO Monica project: Risk factors. Int J Epidemiol 1989;18(3):46-55.
6. Yerpude PN, Jogdand KS. A cross sectional study regarding perceptions of risk factors and complications of obesity in female medical students of South India. Int J Health Sci Res. 2014;4(7):15-18.
7. Legato M J. Gender specific aspects of obesity. Int. J. Text Women's Med 1997;42(3):184-197.

8. Mishra A, Pandey RM, Rema Devi. High prevalence of Diabetes, obesity and Dyslipidaemia in urban slum population in Northern India. Int. J. Obesity. 2001;25:1722-99.
9. Jelliffe BD. The assessment of the nutritional status ofthe Community. Geneva, World Health Organization. 1966;63-78.
10. Priya D, Prasanna KS, Sucharitha K, Vaz NC. Body Image Perception and Attempts to Change Weight among Female Medical Students at Mangalore. Indian J Community Med. 2010;35(2):316–20.
11. Augustine LF, Poojara. Prevalence of obesity, weight perceptions and weight control practices among college girls. Ind. J. Comm. Medi 2003;25(4):189-90.
12. Sekar V, Anil C. Mathew, Thomas V. Chacko. Awareness of women about complications and causes of obesity a cross sectional study in Coimbatore, South India, South Asian journal of preventive cardiology 2009;4(2):27-34.
13. Sung RY, Yu CW, So RC, Lam PK, Hau KT. Self-perception of physical competences in preadolescent overweight Chinese children. Eur J Clin Nutr. 2005;59:101-6.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
International Journal of Health Sciences & Research, 4(7): 15-18, 2014.
Available: https://www.ijhsr.org/archive_ijhsr_vol.4_issue7.html

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1378

Chapter 10
Print ISBN: 978-81-976653-0-1, eBook ISBN: 978-81-976653-1-8

A Review of Epidemiology of Viral Hemorrhagic Fever

Yash Srivastav [a++*], Mohd. Faijan Mansoori [a] and Vipin Kumar Pandey [b]

DOI: https://doi.org/10.9734/bpi/dhrni/v1/1511

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1511

ABSTRACT

The pathophysiology, aetiology, diagnosis, treatment, symptoms, and indicators of virus hemorrhagic fevers (VHFs) are all covered in this review article. Acute zoonotic diseases known as viral hemorrhagic fevers (VHFs) initially appear to be related to platelet malfunction or destruction. The term "Viral Hemorrhagic Fever" (VHF) describes a severe feverish sickness characterized by aberrant vascular control, vascular damage, and hemorrhagic symptoms. Multiple viruses belonging to distinct families are the cause of this illness. The viruses that cause VHF are categorized into seven distinct families according to the International Committee on Taxonomy of Viruses' most recent classification: Hantaviridae, Nairoviridae, Filoviridae, Phenuiviridae, Paramyxoviridae, Arenavidae, and Flaviviridae are the families involved. The concept of virus hemorrhagic fevers (VHFs) originated in the 1930s when Soviet researchers were studying hantaviral hemorrhagic fever (HF) with renal dysfunction. Dengue fever/Dengue haemorrhagic fever and Kyasanur forest sickness are the two most common viral hemorrhagic fevers (VHF) in India, that are transmitted by arthropod vectors. There is currently no effective cure for VHFs. Some people have responded well to ribavirin treatment for Lassa fever or HFRS. The diagnosis of community-acquired pneumonia (CCHF) in India is greatly hampered by the co-occurring symptoms of hemorrhagic fevers such as dengue, Kyasanur forest sickness, Hantavirus hemorrhagic fever, and other illnesses such as leptospirosis, meningococcal infections, and malaria. The pathophysiologic features of VHF include microvascular instability, increased vascular permeability, and poor hemostasis, albeit the underlying processes differ depending on the virus. Additional randomized controlled studies are needed to find out more about the

[a] *Azad Institute of Pharmacy & Research, Lucknow, U.P, India.*
[b] *School of Pharmacy, Sangam University, Bhilwara, Rajasthan, India.*
[++] *Assistant Professor;*
**Corresponding author: E-mail: neelashsrv76@gmail.com;*

best way to treat viral hemorrhagic fevers (VHFs). We want to investigate viral hemorrhagic fevers (VHFs) further.

Keywords: Virus hemorrhagic fevers (VHFs); epidemiology; etiology; pathogenesis; management.

1. INTRODUCTION

Viral Hemorrhagic Fever represents a challenging problem for global health, considering that effective treatments or vaccines are currently unavailable for the majority of the viruses causing VHFs. Understanding the disease pathogenesis of VHF could provide an effective means for treating and monitoring the disease outcome [1,2]. Acute zoonotic diseases known as viral hemorrhagic fevers (VHFs) initially appear to be related to platelet malfunction or destruction [3]. This zoonotic infection is the result of exposure to the virus-contaminated aerosols. Most of the viruses implicated in these diseases require vectors for transmission to humans, with the majority being arthropod-borne or rodent-borne infections [4]. Soviet researchers were examining hantaviral hemorrhagic fever (HF) with renal syndrome in the 1930s, they developed the idea of virus hemorrhagic fevers (VHFs). Later on, these investigators expanded the categorization to encompass Omsk HF and Crimean-Congo HF. The four taxonomic families Arenaviridae, Bunyaviridae, Filoviridae, and Flaviviridae are among the 23 enveloped RNA viruses that cause the diseases included in the VHF. These viruses are similar in that their genetic material is encased in single-stranded RNA, they target primary dendritic, monocyte, and macrophage cells, they replicate cytoplasmically, and they cause symptoms related to the gastrointestinal tract and nervous system. Elevated blood viremia levels and severe cases are related [5]. Though numerous arthropods and rodents act as efficient reservoirs for viral transmission, humans are thought to be the accidental hosts. Humans can contract VHF from arthropod bites or indirectly from contaminated bodily fluids (saliva, urine, faeces, and other fluids) from patients who are experiencing the disease. Viruses that cause VHFs often have a zoonotic life cycle and are limited in their geographic range. An illness known as "viral hemorrhagic fever" in humans, which is brought on by certain viruses such as the Lassa, Dengue, Ebola, and Crimean-Congo hemorrhagic fever viruses, is frequently linked to an unclear shock syndrome. All these viruses, however, appear to be directed both directly and indirectly towards the vascular system, and specifically towards the vascular endothelium [6]. Except for the Ebola virus (EBOV), reservoirs for all four of the viral families are known to exist in zoonoses. Although fruit bats are thought to be the reservoir, only EBOV viral sequences and serological evidence have been found [7]. The bulk of the viruses linked to these illnesses are arthropod- or rodent-borne infections, meaning that they need vectors to be transmitted to humans. These illnesses are typically limited to the endemic regions where their hosts reside due to their zoonotic nature. Nevertheless, these illnesses are no longer exclusive to the regions where they originated due to rising human migration and greater globalization [8,5]. A collection of acute zoonotic illnesses known as viral hemorrhagic fevers (VHFs) have high fatality rates and are brought on by seven distinct virus families that can infect both

people and animals. Hemorrhagic symptoms and, if left untreated, fatal platelet failure are the hallmarks of VHF. The majority of VHF is spread to people by a variety of vectors, including mosquitoes, voles, rats, bats, and ticks. Infections like Dengue, Ebola, Yellow Fever, and Hantavirus are linked to several common and fatal VHF. These illnesses can occasionally result in significant outbreaks and are endemic in a particular region of the world. Worldwide, developing and re-emerging VHFs continue to pose a serious health risk because of the dismal prognosis and dearth of treatments or vaccinations tailored to address them [9]. Just two viruses are known to regularly cause hemorrhagic fevers in India, out of the twelve that can cause the illness. Crimean Congo hemorrhagic fever (CCHF) and Chikungunya fever [10]. Management: There is currently no effective cure for VHFs. Some people have responded well to ribavirin treatment for Lassa fever or HFRS. Some individuals with EVD or Argentine hemorrhagic fever have responded well to treatment with convalescent-phase plasma. Patients primarily need to use supportive therapy. There is a vaccine to prevent hemorrhagic fever in Argentina. The main focus of prevention efforts is preventing contact with both the host species harbouring the disease and individuals with an acute infection. The goal should be to stop the spread of the virus from person to person if prophylactic measures are ineffective and a case of VHFs does arise. Since rodents are among the hosts that carry the viruses that cause hemorrhagic fever, the following are some methods of disease prevention: managing the rodent population and preventing rodents from residing in or entering houses and offices [11,5].

2. EPIDEMIOLOGY

Diseases carried by rats are linked to viruses in the Arenaviridae family. The New World and Old World viral groups are separated from these viruses. Every virus is associated with rodents found in America, Asia, Europe, and Africa. Contact with mouse urine or droppings can result in infection. Aerosol transmission can also happen when rodent excrement is disturbed and releases virus particles into the atmosphere. Human-to-human infections can also be brought on by some viruses. The arenavirus Lassa virus has been responsible for outbreaks in West Africa that have resulted in up to 50% case fatality rates. The most effective way for this virus to spread is by direct contact with multimammate rats, however, an infection can also happen if rodents are caught to be eaten [12]. Bunyaviruses can cause mild to severe sickness and are spread by arthropods and rodents. Rift Valley fever, hantavirus infections, and Crimean-Congo hemorrhagic fever can all be brought on by these viruses. Since Crimean-Congo hemorrhagic fever is the most common infection in humans that is transmitted by ticks, it is a condition that needs to be taken seriously. This illness is brought on by a Nairovirus, which is indigenous to Asia and Africa and is spread by Ixodid ticks. Exposure to blood or other bodily fluids can also result in transmission, which can cause a serious infection with a high risk of death [13,14,5]. African bats have been shown to harbour filoviruses, which are the perpetrators behind Marburg hemorrhagic sickness and the Ebola virus. Person-to-person transmission is a possibility once humans become sick, particularly in individuals who are providing care for infected patients. The Democratic Republic of the Congo has

seen multiple epidemics of Ebola, with case fatality rates reaching 80% to 90%. In low-income nations, the death rate from Marburg hemorrhagic fever can reach 82%. Arthropods are a common means of transmission for flaviviruses, which can cause a wide variety of diseases. The flavivirus known as dengue is spread by the Aedes aegypti or Aedes albopictus mosquito. Clinically, this virus can cause three different types of dengue fever: severe dengue, dengue with warning signals, and dengue without warning signs. Africa, the Americas, Asia, Australia, Europe, and the Pacific Islands are among the continents where this illness is endemic, encompassing over 100 countries. With more severe morbidity and mortality linked to dengue hemorrhagic fever and dengue shock syndrome, dengue fever has a 0.8% to 2.5% death rate [15–17,5].

3. ETIOLOGY

The viral family that includes the viruses linked to viral hemorrhagic fevers and the illnesses they cause is as follows: Family Arenaviridae: Hemorrhagic fever caused by the Chapare virus (CHPV). Venezuelan hemorrhagic fever is caused by the Guanarito virus (GTOV). Fever caused by the Argentine hemorrhagic virus (JUNV). Fever caused by the Lassa virus (LASV). Lujo hemorrhagic fever is caused by the Lujo virus (LUJV). The cause of lymphocytic choriomeningitis is the lymphocytic choriomeningitis virus (LCMV). The Machupo virus (MACV) causes hemorrhagic fever in Bolivia. Brazilian hemorrhagic fever is caused by the Sabia virus (SABV). The Bunyaviridae family includes the Crimean-Congo hemorrhagic fever virus (CCHFV). Dobrava-Belgrade virus (DOBV) - Renal syndrome accompanied by hemorrhagic fever. Hemorrhagic fever with renal syndrome is caused by the Hantaan virus (HTNV). Hemorrhagic fever with renal syndrome is caused by the Puumala virus (PUUV). Fever caused by the Rift Valley fever virus (RVFV). Hemorrhagic fever with renal syndrome is caused by the Saaremaa virus (SAAV) [5]. Severe fever with renal syndrome is caused by the Seoul virus (SEOV). SNV stands for Sin Nombre virus-Hantavirus pulmonary syndrome. The virus that causes severe fever and thrombocytopenia syndrome (SFTSV) is responsible for severe fever and thrombocytopenia syndrome. Hemorrhagic fever with renal syndrome caused by the Tula virus (TULV). The Ebola virus, or Bundibugyo Ebolavirus (BDBV), belongs to the Filoviridae family. Hemorrhagic fever is caused by the Marburg Marburgvirus (MARV). The Ebola virus disease is known as Sudan ebolavirus (SUDV). The Ebola virus disease is known as Tai Forest Ebolavirus (TAFV). Ebola virus disease: Zaire ebolavirus (EBOV). Family Flaviviridae: DENV-1-4, the dengue virus, causes dengue fever. Forest sickness caused by the Kyasanur Forest sickness Virus (KFDV). Omsk hemorrhagic fever is caused by the Omsk hemorrhagic fever virus (OHFV). Yellow fever virus, or YFV for short [18].

4. PATHOGENESIS

The pathophysiologic features of VHF include microvascular instability, increased vascular permeability, and poor hemostasis, albeit the underlying processes differ depending on the virus. Death frequently comes from a process similar to septic shock, where there is insufficient effective intravascular volume circulating,

which causes cellular malfunction and multiorgan system failure instead of exsanguination [5]. The virus normally replicates in dendritic cells upon inoculation, then spreads to local lymph nodes and subsequently to a wide range of organs, including the liver, spleen, lymph node, lung, adrenal gland, and endothelium, via lymph and blood monocytes. The specific organs most impacted change depending on the VHF. Interaction of viruses with immune cells, particularly macrophages and endothelial cells, causes the cells to become activated and releases an inflammatory vasoactive process that is compatible with the state known as systemic inflammatory response syndrome. Dysfunction of endothelial cells, platelets, and/or coagulation factors may be present in impaired hemostasis. In certain VHFs, disseminated intravas coagulation (DIC) occurs frequently. The extent of tissue damage varies with VHF and may be caused by either apoptosis or necrosis. Certain VHFs may inhibit cardiotropy, which would worsen organ perfusion. Although not proven, hypothesized causes of vascular collapse include necrosis of the pituitary or adrenal glands. The virus is quickly removed from survivors' blood, but it can linger for weeks or months in a few immunologically protected areas, including the gonads, central nervous system, and ocular chambers. The last location can lead to the previously described sexual transmission during convalescence [19,5]. There is a dearth of comprehensive knowledge regarding the pathogenic processes of VHFs. Monocytes, macrophages, dendritic cells, and vascular endothelial cells are important viral target cells. Once infected, these cells can spread to other organs via lymphatics. Studies on experimental viral disease (EVD) have revealed that the viral protein VP35 suppresses the interferon (IFN)-regulatory factor 3, which is essential for the production of IFN α/β and antiviral immune responses. Multiorgan failure, oedema, coagulopathy, shock, tissue necrosis, and endothelial damage are caused by extensive cytokine activation and tissue factor release [20]. Most fatal cases of VHFs do not mount a strong antibody response, which may be owing to virus-induced inhibition of the host adaptive immune response. The pathophysiology of most VHFs appears to be connected to unregulated viremia. During acute sickness, the virus can be detected in a broad range of bodily fluids, including blood, saliva, stool, and breast milk. Usually minor, inflammatory cell infiltration consists of a mixture of neutrophils and mononuclear cells. Nonetheless, the host immune response may be harmful in cases of dengue, yellow fever, and hantavirus infections, in which viremia is typically resolved prior to the most severe stage of the illness [5]. The distinct mechanism known as antibody-mediated enhancement could potentially contribute to the onset of dengue hemorrhagic fever [19].

5. VIRAL HEMORRHAGIC FEVER SIGNS AND SYMPTOMS

The initial classification of VHFs was based on the shared signs and symptoms of the underlying disease processes. Initial symptoms of the disease may resemble those of other prevalent tropical illnesses including typhoid and malaria, such as fever and general malaise. Even after the fulminant illness process has commenced, diagnosing VHF remains challenging due to its rarity and indiscriminating symptoms [5]. Differentiating VHF from other tropical diseases is crucial for appropriate therapy of concomitant infections and/or VHF,

as well as for isolation and infection control measures that can help halt the disease's spread. Numerous teams have examined standard laboratory measures to see if certain values may be used to distinguish VHF from other illnesses. Patients with hemorrhagic fever with renal syndrome (RTS) caused by the Hantaan and Seoul viruses had elevated blood urea nitrogen and creatinine, while patients infected with the Huaiyangshan hemorrhagic fever virus showed increased ALT and creatine kinase levels [21]. Patients with EBOV, Sudan virus illness, and CCHFV have been reported to have leukopenia, thrombocytopenia, and elevated levels of ALT and aspartate aminotransferase (AST). Haematological parameters in Dengue hemorrhagic fever endemic areas showed that elevated ALT and aspartate aminotransferase, normal prothrombin time, prolonged activated partial thromboplastin time, and platelet counts of less than 100 ×109/L are useful in assessing the possibility of Dengue hemorrhagic fever. Research has indicated that a high quantity of C-reactive protein (>5 mg/L) is a better indicator of malaria than Dengue hemorrhagic fever. Research has indicated that a high quantity of C-reactive protein (>5 mg/L) is a better indicator of malaria than Dengue hemorrhagic fever [22–25,5]. The diagnosis of VHF cannot be made with great specificity using these test data. However, laboratory markers may provide direction and guidance for identifying individuals with VHF in areas where direct diagnostic tools are not easily accessible. More precise and sensitive ways of identifying VHF have been shown in lab techniques that use patient specimens to directly detect viruses or the humoral immune response to them. Immunoglobulin M (IgM) and IgG specific to viruses can be measured in patient serum using serological markers, which provide a potential disease marker without the logistical and technical limitations of the gold standard of molecular detection. For Lassa fever, the early detection of IgM for Lassa virus (LASV) and IgG for Rift Valley fever virus (RVFV) infections has been successfully demonstrated [26,27,5].

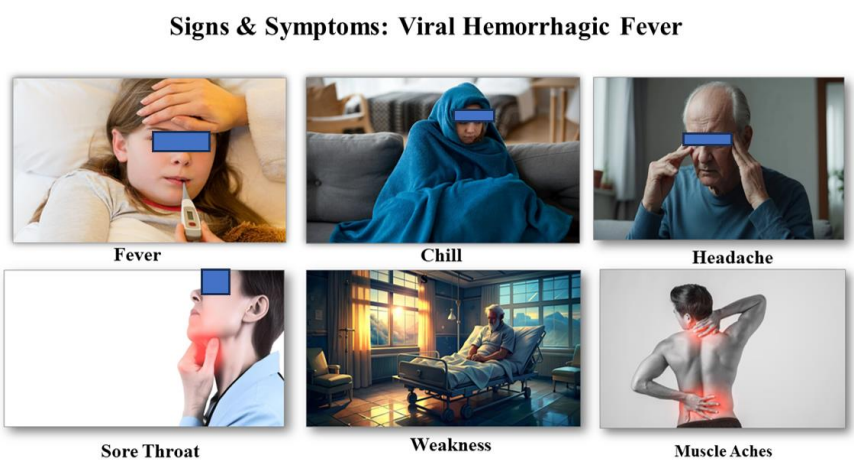


Fig. 1. Signs and symptoms of viral hemorrhagic fever

6. INSPECTION OF RISK

In the form of an assessment algorithm, the Advisory Committee for Dangerous Pathogens (ACDP) has released guidelines for risk assessment of patients with possible VHF. A local infection expert should be consulted if there is any doubt as to whether the patient should be classified as having a "high possibility of VHF" or "low possibility of VHF." Keep in mind that "high possibility" does not equal "high probability." Rather, an alternate diagnosis is far more likely if there has been no contact with any deceased or ill individuals or any other exposure related to the locally significant VHF(s) [28,5].

7. DIAGNOSIS

The comprehensive metabolic panel, type and cross, coagulation studies, liver function tests, complete blood count with differential, and evaluation for bacterial infections with urinalysis, urine culture, chest x-ray, and blood cultures are all part of the clinical evaluation for viral hemorrhagic fevers. IgM and IgG specific to viruses can be detected by serological testing, which is useful but not as sensitive or precise as molecular testing. Techniques for diagnostic testing include the use of reverse transcriptase-polymerase chain reaction and virus isolation by cell culture [18,5]. In a patient with a compatible clinical history and within 21 days of a plausible epidemiological exposure, leucopenia, thrombocytopenia, and transaminitis (aspartate transaminase (AST) > alanine transaminase (ALT)) are suggestive of VHF, especially when the malaria film is negative. According to new ACDP guidance, similar investigations should be carried out as soon as possible in the nearby laboratory, if it is safe to do so and standard precautions (as well as extra splash measures when needed) are followed. Viralemia starts on the first day of fever and lasts the entire duration of the illness. IgM and IgG start to show up on days 3 and 7, respectively, however, there is a chance that there will be a delay in antibody formation, which is linked to a worse prognosis [24,29,30]. Reverse transcription polymerase chain reaction (PCR), which is extremely sensitive and specific and can be used on blood, urine, and saliva/throat swabs, is the method used in laboratory diagnostics. Testing is coordinated by communication between the Imported Fever Service, located at the Rare and Imported Pathogens Laboratory in Salisbury, and local infection specialists. Currently, serological testing is not done on a regular basis in the United Kingdom. Only in containment level 4 laboratories—for epidemiological or research purposes—is viral culture carried out [20]. Laboratory staff may experience anxiety when diagnosing VHF because they worry about getting sick while handling infectious specimens. Gamma irradiation and RNA extraction procedures can be used to inactivate laboratory specimens in places with the necessary resources, such as heat and detergent [5]. Procedures for the appropriate use of protective equipment and training have helped to stop transmission during VHF epidemics and, consequently, reduce transmission to laboratory personnel, even in the absence of inactivation [31].

8. MANAGEMENT OF HEMORRHAGIC VIRAL FEVERS

Early diagnosis is crucial for the appropriate therapy of patients suspected of having viral hemorrhagic fever, as it can boost survival rates and avert nosocomial infections. All personnel who provide care for individuals under investigation should wear appropriate personal protective equipment (also known as viral hemorrhagic fever isolation precautions), and patients exhibiting symptoms or a travel history suggestive of these diseases should be isolated. Although therapy research is still in progress, supportive care is the mainstay of modern treatment. For the diseases with the greatest rates of overall mortality, see the specific management advice listed below [18]. Since more than 25 years ago, ribavirin—an antiviral medication-has been used to treat patients with Lassa fever [5]. It is currently advised for the prevention and treatment of arenaviruses and bunyaviruses. Furthermore, ribavirin-treated patients in a randomized double-blind placebo-controlled experiment with 242 patients in the People's Republic of China who had serologically proven Hantan virus had a seven-fold lower death rate; however, these findings were not supported by further research. Although inconsistent outcomes from the treatment of CCHF patients in Iran and Turkey have been recorded, ribavirin was also proven to be effective against the CCHF virus in vitro. As potential antiviral medications for various VHFs, pyrazine carboxamide compounds like T-705 (favipiravir), T-1105, and T-1106 are being studied in vitro and in vivo. In animal models, these drugs have demonstrated good action against West Nile virus, Junin virus, arenaviruses, bunyaviruses, and Rift Valley Fever (RVF). A novel compound called FGI-106 has demonstrated broad-spectrum antiviral activity [5]. Strong in vitro activity was demonstrated by FGI-106 against a number of deadly infections, including the Dengue, RVF, and Ebola viruses. Furthermore, it was discovered that FGI-106 shielded animals against a fatal challenge in a mouse model of Ebola virus infection. In order to identify new candidate compounds for VHF treatment, high-throughput screening (HTS) of tiny molecular libraries has lately become a viable and innovative method [32]. To evaluate the antiviral activity and possible cytotoxicity of chemical compounds against the Dengue virus, an automated HTS system that is integrated with optical microscopy has been put into place. This method evaluated the cytotoxicity of 5,632 compounds against the Dengue virus type 2 and its antiviral efficacy on human HEK293 [5]. Thus, 73 compounds that showed substantial antiviral activity and no cytotoxicity were recognized as promising candidates for additional in vivo studies. Filoviruses and arenaviruses are examples of BSL-4 pathogens that have been treated with HTS technology through the use of replication-incompetent virus pseudotypes. Strong entrance inhibitors against the Lassa, Junin, Sabia, Machupo, and Guaranito viruses were found during arenavirus research [33–35]. By using the HTS method, entrance inhibitors for filoviruses were also discovered. Specifically, a derivative of benzodiazepines was found to have a 50% inhibitory concentration for the Ebola and Marburg viruses, respectively, of 10 μM and 12 μM. HTS has also been used to study chemicals that could influence the interaction between a virus and its host. Specifically, PF-429242, an amino pyrrolidine molecule, has recently been found to function as a strong inhibitor of SKI-1/S1P, a cellular protease that is necessary for the processing of viral envelop protein precursors. Due to its strong

stability, low toxicity, and unique pharmacokinetic characteristics, this chemical is a promising therapeutic candidate for infections caused by CCHF and arenaviruses [36–39,5].

Although research has been limited, it has been demonstrated that treating the Lassa virus early in the disease phase improves treatment outcomes when administered ribavirin. Currently undergoing evaluation are more recent medicines such as favipiravir and monoclonal antibodies specific to LASV. As of right now, there are no viable Lassa fever vaccinations. The majority of the treatment for Crimean-Congo hemorrhagic fever is supportive. In vitro, ribavirin has shown antiviral activity against this virus. As of now, there is no human vaccine that works. It is advised that those who work in agriculture or with animals wear bug repellent and stay away from potentially contaminated blood and other fluids from humans or other animals. Supportive care is part of the treatment for Marburg hemorrhagic fever and the Ebola virus disease. As of now, there are no vaccinations against the Marburg virus [5]. As of right now, only one Ebola vaccination against the Zaire ebolavirus has received FDA approval. Since there aren't any effective antiviral regimens for dengue fever at the moment, supportive care is the mainstay of management. In Southeast Asia and Latin America, there is now only one vaccine available. The World Health Organization, however, advises against giving it to anyone who hasn't previously contracted dengue [12,15,40–43]. Other than EBOV, there is currently no particular vaccine, medication, or therapeutic approach available for viral hemorrhagic fevers. Recently, two treatment medications for Ebola Zaire were approved by the Food and Drug Administration (FDA). The first medication to be approved was Inmazeb, a mixture of three monoclonal antibodies, in October 2020. The second medication, approved in December 2020, is a monoclonal antibody called Ebanga (Research 2021). Additionally, Merck has produced the rVSVΔG-ZEBOV-GP Ebola vaccine (brand name Ervebo), which was approved by the FDA in 2019 [44].

9. CONCLUSION AND FUTURE DIRECTION

The indications and manifestations of viral hemorrhagic fevers (VHFs), in addition to their aetiology, pathophysiology, epidemiology, diagnostics, and current treatments, are all covered in great detail in our review articles. While pharmaceutical treatments offer benefits, they often come with drawbacks as well, such as kidney damage. Additional randomized controlled studies are needed to find out more about the best way to treat viral hemorrhagic fevers (VHFs). We want to investigate viral hemorrhagic fevers (VHFs) further [5]. A second study involving counselling will be conducted in our nation or state with the help of our colleagues to evaluate the mental and physical health of patients and to give a more thorough understanding of viral hemorrhagic fevers (VHFs) and their improved treatment.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of manuscripts.

ETHICAL STATEMENT

Discriminatory practices act that undermine commitment to these patients' best interests, and conduct or work environments that impair professional judgment are all avoided by pharmacists.

INFORMED CONSENT

Using websites, review articles, and other sources to produce research content.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Iannetta M, Di Caro A, Nicastri E, Vairo F, Masanja H, Kobinger G, Mirazimi A, Ntoumi F, Zumla A, Ippolito G. Viral hemorrhagic fevers other than Ebola and Lassa. Infectious Disease Clinics. 2019 Dec 1;33(4):977-1002.
2. Mariappan V, Pratheesh P, Shanmugam L, Rao SR, Pillai AB. Viral hemorrhagic fever: molecular pathogenesis and current trends of disease management-an update. Current research in virological science. 2021 Jan 1;2:100009.
3. Zapata JC, Cox D, Salvato MS. The role of platelets in the pathogenesis of viral hemorrhagic fevers. PLoS Negl Trop Dis. 2014;8(6).
4. Sehgal A, Mehta S, Sahay K, Martynova E, Rizvanov A, Baranwal M, Chandy S, Khaiboullina S, Kabwe E, Davidyuk Y. Hemorrhagic fever with renal syndrome in Asia: history, pathogenesis, diagnosis, treatment, and prevention. Viruses. 2023 Feb 18;15(2):561.
5. Srivastav Y, Kumar A, Singh J, Srivastav A, Ahmad M. Compendium: Management of Viral Hemorrhagic Fever (Viral Fever), Involving Its Pathogenesis. Asian Journal of Research in Infectious Diseases. 2024 Mar 23;15(3):17-25.
6. Schnittler HJ, Feldmann H. Viral hemorrhagic fever - A vascular disease? Thromb Haemost. 2003;89(6):967–72.
7. Leroy EM, Kumulungui B, Pourrut X, Rouquet P, Hassanin A, Yaba P, et al. Fruit bats as reservoirs of Ebola virus. Nature. 2005;438(7068):575–6.
8. Rodas CMR and JD. Epidemiological surveillance of viral hemorrhagic Fevers with Emphasis on Clinical Virology. 2018;1604.

9. Mariappan V, Pratheesh P, Shanmugam L, Rao SR, Pillai AB. Viral hemorrhagic fever: Molecular pathogenesis and current trends of disease management-an update. Curr Res Virol Sci [Internet]. 2021;2:100009. Available:https://www.sciencedirect.com/science/article/pii/S2666478X21000039
10. Bhalla DA. Association of Physicians of India Indian College of Physicians. Vol. 100.
11. Samaranayake L, Scully C, Nair RG, Petti S. Viral haemorrhagic fevers with emphasis on Ebola virus disease and oro-dental healthcare. Oral Dis. 2015;21(1):1–6.
12. Asogun DA, Günther S, Akpede GO, Ihekweazu C, Zumla A. Lassa Fever: Epidemiology, Clinical Features, Diagnosis, Management and Prevention. Infect Dis Clin North Am. 2019;33(4):933–51.
13. Hidalgo J, Richards GA, Jiménez JIS, Baker T, Amin P. Viral hemorrhagic fever in the tropics: Report from the task force on tropical diseases by the World Federation of Societies of Intensive and Critical Care Medicine. J Crit Care [Internet]. 2017;42:366–72. Available:https://doi.org/10.1016/j.jcrc.2017.11.006
14. Bente DA, Forrester NL, Watts DM, McAuley AJ, Whitehouse CA, Bray M. Crimean-Congo hemorrhagic fever: History, epidemiology, pathogenesis, clinical syndrome and genetic diversity. Antiviral Res [Internet]. 2013;100(1):159–89. Available:http://dx.doi.org/10.1016/j.antiviral.2013.07.006
15. Iannetta M, Di Caro A, Nicastri E, Vairo F, Masanja H, Kobinger G, et al. Viral Hemorrhagic Fevers Other than Ebola and Lassa. Infect Dis Clin North Am. 2019;33(4):977–1002.
16. Rougeron V, Feldmann H, Grard G, Becker S, Leroy EM. Ebola and Marburg haemorrhagic fever. J Clin Virol [Internet]. 2015;64:111–9. Available:http://dx.doi.org/10.1016/j.jcv.2015.01.014
17. Kularatne SAM. Dengue fever. BMJ. 2015;351(September):1–10.
18. Mangat R, Louie T. Viral Hemorrhagic Fevers. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available:https://www.ncbi.nlm.nih.gov/books/NBK560717/. 2024;560717.
19. Bausch DG. 194 . Viral hemorrhagic fevers. 2019;
20. Fhogartaigh CN, Aarons E. Viral haemorrhagic fever. Clin Med J R Coll Physicians London. 2015;15(1):61–6.
21. Chen ZH, Qin XC, Song R, Shen Y, Chen XP, Wang W, et al. Co-circulation of multiple hemorrhagic fever diseases with distinct clinical characteristics in Dandong, China. PLoS One. 2014;9(2).
22. Liu JW, Lee IK, Wang L, Chen RF, Yang KD. The usefulness of clinical-practice-based laboratory data in facilitating the diagnosis of dengue illness. Biomed Res Int. 2013;2013.
23. Kraft CS, Hewlett AL, Koepsell S, Winkler AM, Kratochvil CJ, Larson L, et al. The Use of TKM-100802 and Convalescent Plasma in 2 Patients with Ebola Virus Disease in the United States. Clin Infect Dis. 2015;61(4):496–502.

24. Rollin PE, Bausch DG, Sanchez A. Blood chemistry measurements and D-dimer levels associated with fatal and nonfatal outcomes in humans infected with Sudan Ebola virus. J Infect Dis. 2007;196(SUPPL. 2).
25. Epelboin L, Boullé C, Ouar-Epelboin S, Hanf M, Dussart P, Djossou F, et al. Discriminating Malaria from Dengue Fever in Endemic Areas: Clinical and Biological Criteria, Prognostic Score and Utility of the C-Reactive Protein: A Retrospective Matched-Pair Study in French Guiana. PLoS Negl Trop Dis. 2013;7(9).
26. Bukbuk DN, Fukushi S, Tani H, Yoshikawa T, Taniguchi S, Iha K, et al. Development and validation of serological assays for viral hemorrhagic fevers and determination of the prevalence of rift valley fever in Borno State, Nigeria. Trans R Soc Trop Med Hyg. 2014;108(12):768–73.
27. Ibekwe T, Nwegbu M, Okokhere P, Adomeh D, Asogun D. The sensitivity and specificity of Lassa virus IgM by ELISA as screening tool at early phase of Lassa fever infection. Niger Med J. 2012;53(4):196.
28. Centre SAC of the HPS. The Management of Viral Haemorrhagic Fevers in Ireland; 2012.
Available:http://www.hpsc.ie/A-Z/Vectorborne/ViralHaemorrhagicFever/Guidance/File,12936,en.pdf
29. Mehedi M, Groseth A, Feldmann H, Ebihara H. Clinical aspects of Marburg hemorrhagic fever. Future Virol. 2011;6(9):1091–106.
30. DA B, NL F, DM W, AJ M, CA W, MB. Crimean-Congo hemorrhagic fever: History, epidemiology, pathogenesis, clinical syndrome and genetic diversity. Antiviral Res [Internet]. 2013;100(1):159–89.
Available:http://0-ovidsp.ovid.com.wam.city.ac.uk/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2013741328
31. Racsa LD, Kraft CS, Olinger GG, Hensley LE. Viral hemorrhagic fever diagnostics. Clin Infect Dis. 2016;62(2):214–9.
32. Ippolito G, Feldmann H, Lanini S, Vairo F, Di Caro A, Capobianchi MR, et al. Viral hemorrhagic fevers: Advancing the level of treatment. BMC Med. 2012;10.
33. Bolken TC, Laquerre S, Zhang Y, Bailey TR, Pevear DC, Kickner SS, et al. Identification and characterization of potent small molecule inhibitor of hemorrhagic fever New World arenaviruses. Antiviral Res. 2006;69(2):86–97.
34. Lee AM, Pasquato A, Kunz S. Novel approaches in anti-arenaviral drug development. Virology [Internet]. 2011;411(2):163–9.
Available:http://dx.doi.org/10.1016/j.virol.2010.11.022
35. Furuta Y, Takahashi K, Shiraki K, Sakamoto K, Smee DF, Barnard DL, et al. T-705 (favipiravir) and related compounds: Novel broad-spectrum inhibitors of RNA viral infections. Antiviral Res. 2009;82(3):95–102.
36. Pasquato A, Rochat C, Burri DJ, Pasqual G, La Torre JC de, Kunz S. Evaluation of the anti-arenaviral activity of the subtilisin kexin isozyme-1/site-1 protease inhibitor PF-429242. Virology [Internet]. 2012;423(1):14–22.
Available:http://dx.doi.org/10.1016/j.virol.2011.11.008

37. Urata S, Yun N, Pasquato A, Paessler S, Kunz S, de la Torre JC. Antiviral Activity of a small-molecule inhibitor of arenavirus glycoprotein processing by the cellular site 1 protease. J Virol. 2011;85(2):795–803.
38. Basu A, Li B, Mills DM, Panchal RG, Cardinale SC, Butler MM, et al. Identification of a small-molecule entry inhibitor for filoviruses. J Virol. 2011;85(7):3106–19.
39. Vincent MJ, Sanchez AJ, Erickson BR, Basak A, Chretien M, Seidah NG, et al. Crimean-congo hemorrhagic fever virus glycoprotein proteolytic processing by subtilase SKI-1. J Virol. 2003;77(16):8640–9.
40. Ollmann Saphire E. A vaccine against ebola virus. Cell [Internet]. 2020;181(1):6.
Available:http://dx.doi.org/10.1016/j.cell.2020.03.011
41. Rougeron V, Feldmann H, Grard G, Becker S, Leroy EM. Ebola and Marburg haemorrhagic fever. J Clin Virol Off Publ Pan Am Soc Clin Virol. 2015 Mar;64:111–9.
42. Kularatne SAM. Dengue fever. BMJ. 2015 Sep;351:h4661.
43. Gubler DJ, Halstead SB. Is Dengvaxia a useful vaccine for dengue endemic areas? BMJ. 2019 Oct;367:l5710.
44. Mariappan V, Pratheesh P, Shanmugam L, Rao SR, Pillai AB. Viral hemorrhagic fever: Molecular pathogenesis and current trends of disease management-an update. Curr Res Virol Sci [Internet]. 2021;2(July): 100009. Available:https://doi.org/10.1016/j.crviro.2021.100009

Biography of author(s)

Mr. Yash Srivastav (Assistant Professor)
Azad Institute of Pharmacy & Research, Lucknow, U.P, India.

He earned a Master of Pharmacy (M. Pharm) in pharmaceutics from the Goel Institute of Pharmacy & Sciences (GIPS), Lucknow, Uttar Pradesh, India, where he finished his post-graduate studies in the pharmacy department. Currently, he teaches at the Azad Institute of Pharmacy and Research as an assistant professor.

Mohd. Faijan Mansoori
Azad Institute of Pharmacy & Research, Lucknow, U.P, India.

He earned a pharmaceutics Master of Pharmacy (M. Pharm). Currently, he is working at the Azad Institute of Pharmacy and Research as an assistant professor.

Vipin Kumar Pandey
School of Pharmacy, Sangam University, Bhilwara, Rajasthan, India.

I serve as an Assistant Professor. I earned my degree from the School of Pharmacy, Sangam University, Bhilwara, Rajasthan, India.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Asian Journal of Research in Infectious Diseases, 15(3): 17-25, 2024. DOI: 10.9734/AJRID/2024/v15i3

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1511

Chapter 11
Print ISBN: 978-81-976653-0-1, eBook ISBN: 978-81-976653-1-8

Early Exposure to Antibiotic Therapy after Common Infections as a Risk Factor for the Development of Respiratory Atopy

Alketa H. Bakiri [a,b#] and Ervin Ç. Mingomataj [c#*]

DOI: https://doi.org/10.9734/bpi/dhrni/v1/1376

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1376

ABSTRACT

Antibiotics are one of the most frequently prescribed medications and their rational use has become an essential topic in clinical care. In this context, we have witnessed a dramatic increase in the prevalence of respiratory allergies during the last decades. The infections' role in the prevalence of respiratory allergic diseases is attributed to the antagonism between: a) induction of T helper (Th) 1 immune response by human organisms; and b) manipulation of the human immune response toward Th2 profile by common infective agents to increase their surviving opportunity. This work proposes that extensive antibiotic exposure during neonatal and early childhood plays an important role in the increasing epidemiological trend. It is believed that antibiotic exposure during early childhood has also provided better survival opportunities for atopic individuals with an inadequate immune defense against common infections, deviating, therefore, from the genetic background of the general population toward the Th2 profile. Considering this, we suggest that Th2 profile frequency (and consequently atopic phenotype prevalence) can be increased along an individual lifespan after extensive antibiotics introduction until the entire population is exposed to them during childhood. This hypothesis may explain findings on epidemiological surveys, which report a prevalence increase among adults in industrialized countries between the 1970s and 2000s; in recently-developed countries, this trend began only at the end of the 1980s. These arguments support the conclusion that infections will manipulate human immunity over generations. In contrast, actual antibiotics can increase the prevalence of respiratory allergies among a population only along with individual longevity. These findings may help develop future management

[a] *American Hospital of Tirana, Outpatients Allergology Service, Tirana, Albania.*
[b] *Faculty of Medical Sciences, Albanian University, Tirana, Albania.*
[c] *Department of Allergy & Clinical Immunology, "Mother Theresa" School of Medicine, Tirana, Albania.*
[#] *Both authors contributed equally to this work;*
**Corresponding author: E-mail: allergology@gmx.de*

strategies to treat respiratory allergic or infective pathologies. The knowledge of the mentioned interactions may help us develop better etiological theories about respiratory allergic diseases that can replace the actual theory or incorporate it as an additional possible scenario.

Keywords: Antibiotic exposure; common infections; early childhood; prevalence trend; respiratory allergies.

1. INTRODUCTION

At the beginning of the 21st century, infectious diseases remain responsible for about one-quarter of deaths worldwide, causing at least 10 million deaths per year, mainly in tropical countries. The global population has witnessed a dramatic increase in the prevalence of respiratory allergies during the last decades. "It is estimated that worldwide 14% of children have asthma and 7.9% have eczema. Estimations for allergic rhinitis (hay fever) worldwide are 20.7% in 6-7 year olds and 33.2% in 13-14 year olds." Antibiotics are one of the most frequently prescribed medications and their rational use has become an essential topic in clinical care. The administration of antibiotics to infants is also very common. In high-income countries, more than half of all infants have had antibiotic treatments during their first months of life [1,2]. This study investigates the role of extensive antibiotic exposure during neonatal and early childhood in the increasing epidemiological trend.

1.1 Respiratory Atopy Trend and Risk Factors

At the beginning of the 20th century, allergies were rare diseases, while the last decades have witnessed a dramatic increase in disease burden and prevalence [3-5]. They represent the most frequent European chronic diseases, affecting more than 60 million people [3]. Data from several sources indicate worldwide increases in bronchial asthma or allergic rhinitis, especially in English-speaking countries [3,4,6]. Thus, during the 1990s, the prevalence of wheezing or bronchial hyperreactivity among European children aged 13-14 years varied from 32.2% in the United Kingdom to only 2.6% in Albania (Fig. 1) [3-5,7-9]. Similar variations within these states are evidenced among adults aged 20-44 [4,10].

In Western countries, the prevalence rising trend has been interrupted, while in developing ones, it continues [11,12]. Furthermore, the prevalence of allergic pathologies has started to subside in some industrialized countries [12]. While the increasing prevalence is largely explained by the influence of environmental factors and epigenetic mechanisms, its recent interruption is not fully explained [11]. The most important components concerning allergy widespread include improved hygienic conditions, decreased exposure to infections, extensive antibiotic use, pollution, traffic exhaust, etc. A consistent proportion of these factors are presumed to be components of “the hygiene hypothesis”, whereas more recently all risk factors are incorporated in “the changing world theory” [12-15].

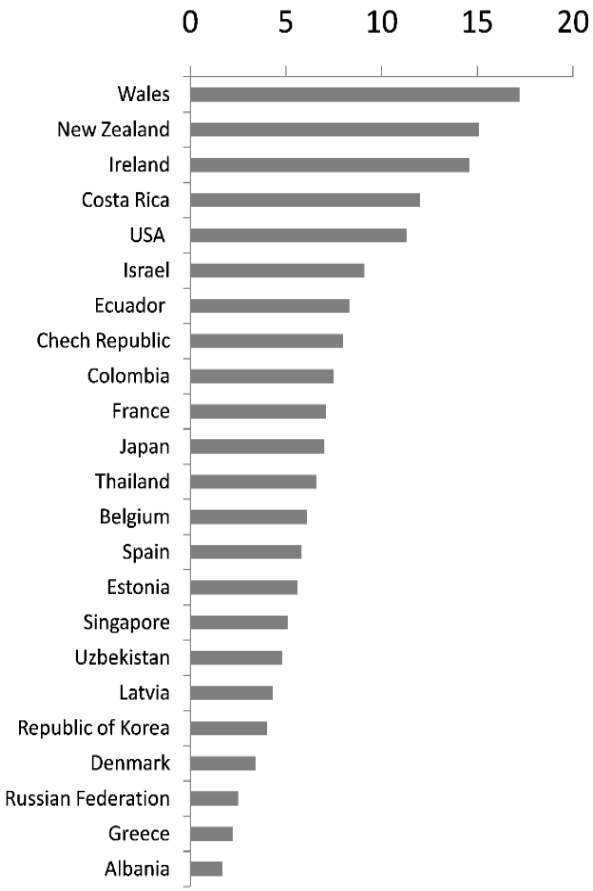


Fig. 1. Asthma prevalence during the end of the 20th century [9,10] Asthma prevalence has varied from 0.5-5% in developing countries to 20-25% in English-speaking countries such as Australia and New Zealand

The identified risk factors for respiratory atopic pathologies cannot equally account for the globally rising prevalence, international patterns, or recent declines in some Western countries [16]. Antibiotic therapy (and its interaction with infections) might be the factor that globally covers the largest human population, compared to other risk factors such as emigration, urban life, improved hygiene, etc. This work aims to elicit the impact of global antibiotic exposure and its interaction with infections on the prevalence trends regarding respiratory allergies.

1.2 The Infections' Role in Respiratory Atopy

According to worldwide knowledge, the infection role in the prevalence of respiratory allergies consists in the antagonism between: a) induction of human T helper (Th) 1 immune response as a consequence of infection; and b) manipulation of this immune response toward Th2 profile by common infective agents to increase the invaders' surviving opportunity [4,17]. On the first hand, it is postulated that antibiotic-induced growth inhibition of the enteric microbiota can suppress the healthy "education" of Th1 immune response in children, leading to a Th2 allergic inflammatory predisposition without changes of genome even after exposure to one antibiotic course along the first life year [4,14,15,18-23]. Apart from microbiota reduction, early infant antimicrobial therapy can cause microbial dysbiosis. This may lead to the inception of allergic diseases, and consequent predisposition for irrational antibiotics' use [23]. On the other hand, different infectious agents can manipulate the host immunity through induction of Th2/immunoglobulin (Ig) E response to increase their survival chances [4,17,24,25]. Thus, the development of hyperreactive respiratory symptoms during common bacterial and viral infections after a "silent" incubatory period suggests that microorganisms may manipulate host immunity, allowing themselves a "safe escape" for a few days, before the host production of eradicative IgA or IgG antibodies [25]. While common microorganisms induce hyperreactive/allergic respiratory symptoms after reproduction, an extensive infestation with various geohelminths in equatorial regions suppresses respiratory symptoms and widespread atopic pathologies despite the potent IgE induction [3,24,26-32]. The negative correlation of infective agent survival to the concentration of specific IgG1 and IgA suggests that *in vivo*, the Th2 profile may not simply be a host-chosen reaction only, but also the most efficient and beneficial humoral response during host-infection interaction [33-36]. Considering that traditional antibiotics cannot eradicate many infections and that actual human populations show a more frequent Th2/IgE profile in association with antibiotics' use, it could be reinforced that the development of bronchial and nasal hyperreactivity after early respiratory infections could be considered a predictor for a future allergic "career" and a consequence of the invaders' manipulatory ability to reassure their reproduction/survivorship [37-39].

1.3 Relationship Antibiotic Exposure – Atopy Trend

Since penicillin discovery by Alexander Fleming in 1928, Australia was the first country to make the drug available for civilian use after World War II, followed by the USA and Western European countries [40]. Extensive antibiotic exposure in the rest of the world happened stepwise within a few decades, and nowadays antibiotics are largely used in common bacterial infections. Worldwide it is believed that affluent life and especially antibiotic exposure have provided supplemental survival possibilities, especially among atopic individuals, declining the mortality rate after common respiratory or gastroenteric infections in early life [41]. This is because broad-spectrum antibiotics may increase survival rates during serious infections in children who fail to provide adequate natural immune response similar to IgA or IgG antibodies [42,43]. In effect, before the antibiotic era, subjects

showing such a response deficit had fewer opportunities to survive, and consequently to have their offspring. In contrast, the massive introduction of broad-spectrum antibiotics promoted relative surviving parity against these infections [4]. The effect of antibiotic exposure among young subjects who predominantly inhered the Th2/IgE profile has possibly enabled the partial deviation of the immune-genetic thesaurus for successive adult populations within a few decades to a more frequent allergy-predisposing genotype. Despite the lack of identified changes, it is not excluded that the frequency of hereditary markers corresponding to the IgE antibody genotype or Th2 profile may also be more frequently shown among respective populations [17]. The missed antibiotic-related survival effect has accounted for increased rates of fatal respiratory infections among South American children of low socioeconomic status, whereas children coming from affluent societies experienced more frequent respiratory allergies or used oftener antibiotics [44]. These findings demonstrate that a large exposure to antibiotics during early life provides much higher survival chances for children who experience serious respiratory and gastrointestinal infections, even if they possess inappropriate natural immune responses [17].

Furthermore, the extensive antibiotic use associated with better living conditions in Western countries could have been the initial factor in the discrepancy of allergy prevalence between industrialized and non-industrialized world [4]. Epidemiological difference first likely corresponds with the time point around 20-25 years after initial extensive antibiotic exposure [13,26]. This time point, in turn, corresponds to a rising prevalence start of respiratory allergies predominantly observed in industrialized countries, particularly over the last 35-40 years of the 20th century [5,45]. Thus, von Mutius et al. have demonstrated that in genetically similar individuals, the prevalence of respiratory allergies was significantly higher among school children living in the former West (Munich) than children of former East Germany (Leipzig and Halle) [5,26,46]. Surprisingly, the mentioned east-west differences are observed only among children and younger adults but not among Germans born before the 1960s, suggesting that a “cohort effect” has been operating with the lifetime allergy risk under the influence of living conditions in early childhood [12,13,26]. In parallel to Western Europe, significant increases in asthma morbidity in the USA have occurred since the 1970s, particularly among immigrants or African-American subjects [4,47]. Compared to Western countries, the rising prevalence of atopic pathologies in the rest of the world is observed later [12,48]. Several studies performed in tropical regions have provided further evidence that atopic disorders occur more commonly among individuals living in urban, more affluent, and westernized areas compared with those living in rural areas with traditional lifestyles [24,26].

The genetic population heterogeneity in English-speaking countries indicates far higher immigration rates (compared to other industrialized states). In contrast, the highest prevalence of asthma symptoms among immigrants can be explained by “the fireside/fireplace hypothesis” [26,49]. Thus, using fire to handle harsh temperature variations since the migration in the northern world regions would have led to more time spent close to smoke – a known air polluter [4,49]. While generations experiencing a more permanent and continuous exposure to smoke

are better protected against airway pathologies, the African-American subjects (originating from equatorial regions) experience more frequent respiratory diseases after exposure to tobacco, traffic, or industrial polluters [4,49]. This is because, during generations, their exposure to fire and smoke was nearly occasional for climatic reasons; hence, adaptation to this pollution is inadequate. Atopic predisposition among immigrant populations of West European countries is reflected in the increased rate of IgE-mediated asthma, while delayed atopy rising prevalence is happening in developing countries [11,12,50]. The increase was more evident in the older age group, suggesting that environmental influences on allergy development may not be limited to early childhood [11].

These data demonstrate that the epidemiological differences in respiratory allergic pathologies between industrialized and recently-developed countries in European subjects born after the 1960s diminished during the 1990s like in the reunified Germany [13,51]. Moreover, general "Westernization" is associated with an increased prevalence of atopic diseases mostly in former lower and mid-income countries. In contrast, Western regions have already reported any increase or even decrease in asthma prevalence over the last 10-15 years [8-12,14-16,23,48].

The divergent prevalence trends regarding allergic diseases need more research to find the real causes [3,8]. Concerning the significant role of extensive antibiotic exposure, differences in respiratory allergy affection may reflect the timing of the initial event: a higher prevalence could correspond to earlier massive antibiotic use (Fig. 2) [4,9,13,17,26,52]. According to our postulation of 2015, the diminishing prevalence trend for respiratory allergies in industrialized countries indicates that the antibiotic impact on atopy wide-spreading may continue for active individual longevity (periods of childhood and fertile adulthood of the first interested generation). This period in industrialized countries begins with introductory antibiotic exposure after World War II with respective consequences first observed after the 1960s, and finishes during the 2000s (about 60 years after the initial antibiotic use) with interruption of the atopy rising trend [4,13,17,26,52]. In contrast, the epidemiological trend in the recently developed countries (where antibiotic use began later) started to reduce epidemiological differences with Western ones [11-13,16,17,51]. Nevertheless, the intensity and mosaic of risk factors for respiratory allergies vary between various countries, while the actual strategy for antibiotics use among children is quite different from the previous century. We expect the actual epidemiological allergy trend will be a reality in recently developed countries, showing variable and lower tendencies compared to Western ones during the last century, as long as actual antibiotics' application is not so extensive as observed in antecedent decades [17,52]. Some current reports about average atopy prevalence values in recently-developed Asiatic countries, consideration of certain infections or antibiotic use during the first life year risk factors for respiratory allergies, and the increased respiratory atopy burden among metropolitan immigrants in a European industrialized country support our reflections, being an indicator for the confluent trend between different populations [53-55].

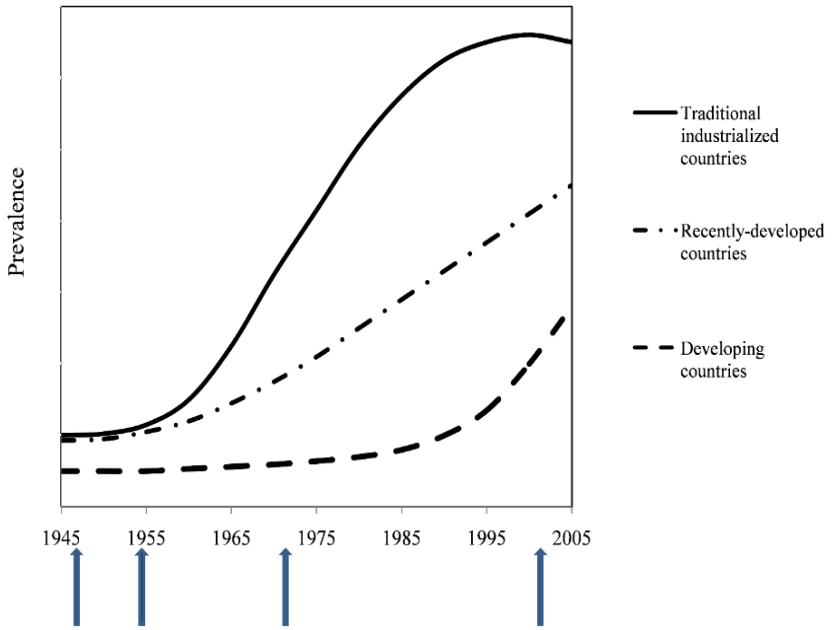


Fig. 2. Asthma prevalence trend and introduction to antibiotics [9]
Three different asthma prevalence trends (high, intermediate, and low) are distinguishable, and developed under the interaction of several risks and protection factors. Initial antibiotic exposure is shown via three arrows (respectively beginning from the left). The beginning of prevalence discrepancies in adults corresponds with a time point about 20 years after antibiotic exposure (first arrow from the left). This could be explained by the fact, that in industrialized countries, antibiotics' surviving role for the Th2-born populations during early childhood is reflected in the population's genome of adults during the 1960s-1970s. This effect is shown later in recently industrialized countries (second arrow from the left) and much later in developing ones (third arrow from the left), which reflects the time point of antibiotic exposure in the population's early childhood. The arrow on the right represents the time point when all adults in industrialized countries are exposed to antibiotics during their early childhood and have offspring until the early 2000s. This time point corresponds to the end of discriminating influence for antibiotic exposure and possibly for "the hygiene hypothesis". The equivalent time point for the rest of the world should be within the next decade, but the highest asthma prevalence will not necessarily be equal to industrialized countries because of actual strategies on the antibiotics use limitation.

Maybe one decade later, antibiotic exposure will no longer be a discriminating risk factor for asthma and atopy among populations of recently developed countries, including the important period between 0 and 1 year of age [15]. This concept, in concert with other established risk factors, can explain the increased allergy prevalence in industrialized countries among autochthonous populations, including the divergent trends in the prevalence of respiratory allergies between them and populations of recently developed countries. In addition, our suggestion may explain why the subside of a widespread increase in industrialized countries occurred just about 20 years ago, which nearly corresponds to the above-mentioned human life cycle (childhood + fertile lifespan) since respective antibiotic exposure. The antibiotics' influence on the lifelong period since first exposure, especially during the first life year, agrees with the fact that they are considered a risk factor for asthma in children in previous decades, while this concept is likely to be considered false in studies originating from industrialized countries [14,15,17,18,48]. If true, this epidemiological pattern will occur in every (recently developed) country at a certain time. Considering the above concept, “the hygiene hypothesis” should play a role in the rising prevalence trend until the entire population is exposed to antibiotics during early childhood and not necessarily until it will get such an increased prevalence for respiratory allergies as in Western countries.

2. CONCLUSIONS

- Antibiotic exposure and internal microbiota reduction are synergistic factors for the induction of the atopic response, affecting the largest populations as the major components of “the hygiene hypothesis” and “the changing world theory”.
- In this context, antibiotics behave not only as suppressors of immune “education” but also as “lucky devils” for relatively “immuno-deficient” Th2-born subjects during their early life, assuring a possible deviation of populations’ genetic background toward the Th2/IgE profile.
- This work explains the discrepancy between the actual increase of respiratory allergy prevalence in recently developed countries and its deceleration in Western countries (where this trend is slowed down or interrupted). It argues that antibiotic exposure could be involved in the respiratory allergy widespread only for a period of an individual’s life longevity. The finish of this period corresponds to experiencing antibiotic exposure and surviving common childhood infections in all populations.
- Finally, the knowledge of the mentioned interactions may help us develop better etiological theories about respiratory allergic diseases that can replace the actual theory or incorporate it as an additional possible scenario.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Fenollar F, Mediannikov O. Emerging infectious diseases in Africa in the 21st century. New Microbes and New Infections. 2018;26:S10-8.
2. Baron R, Taye M, der Vaart IB, Ujčič-Voortman J, Szajewska H, Seidell JC, Verhoeff A. The relationship of prenatal antibiotic exposure and infant antibiotic administration with childhood allergies: A systematic review. BMC Pediatrics. 2020;20:1-4.
3. Papadopoulos NG, Agache I, Bavbek S, et al.Research needs in allergy: An EAACI position paper, in collaboration with EFA. Clin Transl Allergy. 2012;2:21.
4. Mingomataj E. Changing world as principal reason for atopy rising trend. Int J Asthma Allergy Immunol. 2007;5:2.
5. Bjorksten B, Dumitrascu D, Foucard T, et al. Prevalence of childhood asthma, rhinitis and eczema in Scandinavia and Eastern Europe. Eur Respir J. 1998;12:432-7.
6. Davies RJ, Rusznak C, Devalia JL. Why is allergy increasing? - Environmental factors. Clin Exp Allergy. 1998;28:8-14.
7. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee: Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet. 1998;351:1225-32.
8. Asher MI, Montefort S, Bjorksten B, et al. ISAAC phase three study Group: Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368:733–43.
9. Bull World Health Organ. Genebra Jul. 2005;83(7). Available:http://www.who.int/bulletin
10. The European Community Respiratory Health Survey: Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). Eur Respir J. 1996;9:687-93.
11. Björkstén B, Clayton T, Ellwood P, Stewart A, Strachan D; ISAAC Phase III Study Group: Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies in Childhood. Ped Allergy Immunol. 2008;19:110-24.
12. Aubier M, Neukirch F, Annesi-Maesano I. [Epidemiology of asthma and allergies. The prevalence of allergies increases worldwide, and asthma has reached its highest-ever prevalence in Europe: why?]. Bull Acad Natl Med. 2005;189:1419-34.
13. Strachan DP. Family size, infection and atopy: The first decade of the hygiene hypothesis. Thorax. 2000;55:S2-S10.

14. Muc M, Padez C, Pinto AM. Exposure to paracetamol and antibiotics in early life and elevated risk of asthma in childhood. Adv Exp Med Biol. 2013;788:393-400.
15. Heintze K, Petersen KU. The case of drug causation of childhood asthma: Antibiotics and paracetamol. Eur J Clin Pharmacol. 2013;69:1197-209.
16. Pearce N, Douwes J. The global epidemiology of asthma in children. Int J Tuberc Lung Dis. 2006;10:125-32.
17. Mingomataj EÇ, Xhixha F, Gjata E, Hyso E, Qirko E. Prevalence of a family history of atopic disease among 3 generations of atopic respiratory patients in Tirana, Albania. J Invest Allergol Clin Immunol. 2008;18:190-3.
18. Marra F, Lynd L, Coombes M, et al. Does antibiotic exposure during infancy lead to development of asthma? A systemic review and metaanalysis. Chest. 2006;129:610-8.
19. Matricardi PM, Rosmini F, Ferrigno L, et al. Cross-sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus. BMJ. 1997;314:999-1003.
20. Strachan D. Is allergic disease programmed in early life? Clin Exp Allergy. 1994;24:603-5.
21. Varner AE. The increase in allergic respiratory diseases: Survival for the fittest? Chest. 2002;121:1308-16.
22. McKeever TM, Lewis SA, Smith C, et al. Early exposure to infections and antibiotics and the incidence of allergic disease: A birth cohort study with the West Midlands General Practice Research Database. J Allergy Clin Immunol. 2002;109:43–50.
23. Tramper-Stranders G, Ambrożej D, Arcolaci A, et al. The EAACI Task Force Conscious, rational use of antibiotics in allergic diseases. Dangerous liaisons: Bacteria, antimicrobial therapies, and allergic diseases. Allergy. 2021;76:3276–91.
24. Mingomataj EC, Xhixha F, Gjata E. Helminths can protect themselves against rejection inhibiting hostile respiratory allergy symptoms. Allergy. 2006;61:400-6.
25. Mingomataj EÇ, Rudzeviciene O. From latent incubation launched into hostile symptomatic pathology: A probable survival strategy for common respiratory infectious agents. Med Hypotheses. 2007;68:397–400.
26. Von Hertzen LC, Haahtela T. Asthma and atopy - the price of affluence? Allergy. 2004;59:124-37.
27. Lynch NR, Hagel IA, Palenque ME, et al. Relationship between helminthic infection and IgE response in atopic and nonatopic children in a tropical environment. J Allergy Clin Immunol. 1998;101:217–21.
28. Bakiri AH, Mingomataj EÇ. Parasites-induced skin allergy: A strategic manipulation of the host immunity. J Clin Med Research. 2010;2:247-55.
29. Bakiri AH, Mingomataj EÇ. Urticaria as symptom of parasite migration through the biological barriers. Open Allergy J. 2011;4:1-7.
30. Flohr C, Quinnell RJ, Britton J. Do helminth parasites protect against atopy and allergic disease? Clin Exp Allergy. 2009;39:20–32.
31. Hohmann H, Panzer S, Phimpachan C, Southivong C, Schelp FP. Relationship of intestinal parasites to the environment and to behavioral

factors in children in the Bolikhamxay Province of Lao PDR. Southeast Asian J Trop Med Public Health. 2001;32:4–13.
32. Cooper PJ, Chico ME, Bland M, Griffin GE, Nutman TB. Allergic symptoms, atopy, and geohelminthic infections in a rural area of Ecuador. Resp Crit Care Medicine 2003;168:313–7.
33. Paterson S, Wilkes CP, Bleay C, Viney ME. Immunological responses elicited by different infection regimes with Strongyloides ratti. PLoS ONE. 2008;3:e2509.
34. Bleay C, Wilkes CP, Paterson S, Viney ME. Density-dependent immune responses against the gastrointestinal nematode Strongyloides ratti. Int J Parasitol. 2007;37:1501-9.
35. Hübner MP, Pasche B, Kalaydjiev S, et al. Microfilariae of the filarial nematode Litomosoides sigmodontis exacerbate the course of lipopolysaccharide-induced sepsis in mice. Infect Immunol. 2008;76:1668-77.
36. Gottstein B, Piarroux R. Current trends in tissue-affecting helminths. Parasite. 2008;15:291-8.
37. Papadopoulos NG, Christodoulou I, Rohde G, et al. Viruses and bacteria in acute asthma exacerbations–a GA(2)LEN-DARE systematic review. Allergy. 2011;66:458–68.
38. Skevaki CL, Psarras S, Volonaki E, et al. Rhinovirus-induced basic fibroblast growth factor release mediates airway remodeling features. Clin Transl Allergy. 2012;2:14.
39. Jartti T, Korppi M. Rhinovirus-induced bronchiolitis and asthma development. Ped Allergy Immunol. 2011;22:350-5.
40. Sheehan JC, Henery-Logan KR. The Total Synthesis of Penicillin V. J Amer Chem Society. 1957;79:1262–3.
41. Battersby AJ, Gibbons DL. The gut mucosal immune system in the neonatal period. Ped Allergy Immunol. 2013;24:414-21.
42. Hanson LA, Korotkova M. The role of breastfeeding in prevention of neonatal infection. Semin Neonatol. 2002;7:275-281.
43. Belderbos ME, Houben ML, van Bleek GM, et al. Breastfeeding modulates neonatal innate immune responses: A prospective birth cohort study. Ped Allergy Immunol. 2012;23:65-74.
44. Nascimento-Carvalho CM, Rocha H, Benguigui Y. Effects of socioeconomic status on presentation with acute lower respiratory tract disease in children in Salvador, Northeast Brazil. Ped Pulmonol. 2002;33:244-8.
45. Grüber C, Illi S, Plieth A, Sommerfeld C, Wahn U. Cultural adaptation is associated with atopy and wheezing among children of Turkish origin living in Germany. Clin Exp Allergy. 2002;32:526-31.
46. von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. Am J Respir Crit Care Med. 1994;149(2 Pt 1):358-64.
47. Ostro B, Lipsett M, Mann J, Braxton-Owens H, White M. Air pollution and exacerbation of asthma in African-American children in Los Angeles. Epidemiology. 2001;12:200-8.

48. Thomas M, Custovic A, Woodcock A, Morris J, Simpson A, Murray CS. Atopic wheezing and early life antibiotic exposure: A nested case-control study. Ped Allergy Immunol. 2006;17:184-8.
49. Platek SM, Gallup GG Jr, Fryer BD. The fireside hypothesis: Was there differential selection to tolerate air pollution during human evolution? Med Hypotheses. 2002;58:1-5.
50. Ballin A, Somekh E, Geva D, Meytes D. High rate of asthma among immigrants. Med Hypotheses. 1998;51:281-4.
51. von Mutius E, Weiland SK, Fritzsch C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. Lancet. 1998;351:862-6.
52. Bakiri AH, Mingomataj EÇ, Ibranji A. Role of antibiotics and infection-host interactions in the prevalence of respiratory atopy: Experience and perspective. Open Allergy J. 2015;8:1-6.
53. Barne M, Singh S, Mangal DK, et al. Global Asthma Network Phase I, India: Results for allergic rhinitis and eczema in 127,309 children and adults. J Allergy Clin Immunol Glob. 2022;1:51-60.
54. Chinratanapisit S, Suratannon N, Pacharn P, Sritipsukho P, Vichyanond P. Prevalence and risk factors of allergic rhinitis in children in Bangkok area. Asian Pac J Allergy Immunol. 2019;37:232-9.
55. Richter JC, Jakobsson K, Taj T, Oudin A. High burden of atopy in immigrant families in substandard apartments in Sweden - on the contribution of bad housing to poor health in vulnerable populations. World Allergy Organ J. 2018;11:9.

Biography of author(s)

Dr. Alketa H. Bakiri
American Hospital of Tirana, Outpatients Allergology Service, Tirana, Albania and Faculty of Medical Sciences, Albanian University, Tirana, Albania.

She has many years of research and academic experience. She has earned her MD in the year 2021. Her research domain inclines towards allergology and clinical immunology. She has been a lecturer of allergology and clinical immunology. She has published 31 papers in reputed international journals along with 4 book chapters.

Ervin Ç. Mingomataj
Department of Allergy & Clinical Immunology, “Mother Theresa” School of Medicine, Tirana, Albania.

Research and Academic Experience: He is an associate professor in the Department of Allergology, immunology, and Human Histology; moreover, he was a guest scientist (2000-2003) and was promoted at Charité (CVK), Medicine University, Berlin, Germany in the year 2011.

Research Specialization: His research area involves clinical allergist-immunologist.

Number of Published papers: In his 66 international publications, nearly 60 papers were published in reputed journals, along with 6 book chapters.

Any other remarkable point(s): He has been a reviewer and guest associate editor in different international academic journals.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
The Open Allergy Journal, 8: 1-6, 2015. DOI: 10.2174/1874383401508010001

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1376

Chapter 12
Print ISBN: 978-81-976653-0-1, eBook ISBN: 978-81-976653-1-8

Knowledge, Awareness and Practices on Preventive Methods against Mosquito Bite among Households in an Urban Slum Area of South India

Pravin Yerpude [a++*] and Keerti Jogdand [a#]

DOI: https://doi.org/10.9734/bpi/dhrni/v1/1344

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1344

ABSTRACT

Aim: The present community-based study was conducted to assess the knowledge, awareness and practices of mosquito bite prevention methods amongst households in an urban slum area of South India.
Introduction: For the effective control of the diseases transmitted by mosquitoes, efforts have been consistently made to educate the community on the danger of mosquito bites. When it comes to communicable diseases, mosquito-borne illnesses rank highly among India's public health issues. The three most serious ones are dengue fever, chikungunya fever, and malaria. The general community's education about preventing mosquito bites is one of the key elements of the vector-borne disease control program.
Materials and Methods: The present community-based study was conducted in the Guntur district of Andhra Pradesh. All households of Urban Health Training Center, Shrinavasrao Thota which is the urban catchment area of the Department of Community Medicine, Katuri Medical College, Guntur were selected for the study.
Results: 91.50% of the study participants had knowledge about breeding places of mosquitoes. 22.29% of the study population still had myths that garbage was the breeding place for mosquitoes. Only 33.72% of the study population knew that dengue, chikungunya was transmitted by mosquitoes. It was observed that Television was the main source of awareness for the community followed by newspapers, radio, friends and advertisements. It was disappointing to note that

[a] Department of Community Medicine, Chhindwara Institute of Medical Sciences, Chhindwara (M.P.)-480001, India.
[++] Professor and HOD;
[#] Associate Professor;
**Corresponding author: E-mail: drpravinyerpude@gmail.com;*

doctor or health staff was not mentioned as the source of knowledge which are coming in contact with people in day-to-day life.
Conclusion: The study found that knowledge about the causes of malaria and mosquito breeding places was satisfactory in study subjects, but some myths were still prevalent. People should be made aware that mosquito bite causes other diseases also. Insecticide-treated bed-net is a good weapon to fight against mosquito-borne disease and Strong social or commercial marketing of these products can definitely increase the acceptance.

Keywords: Awareness; practice; mosquito bite.

1. INTRODUCTION

Mosquitoes are vectors of a number of contagious and potentially fatal diseases, such as protozoan (Malaria), viral (Chikungunya, West Nile virus, yellow fever, and Japanese encephalitis), or helminthic (Filariasis) infections. The containment and prevention of the spread of vector-borne diseases depend greatly on public education and awareness. In almost all parts of India, community engagement is significantly below expectations, despite several mass media and educational strategies [1]. In India, Mosquito-borne diseases constitute a major public health problem in the list of communicable diseases. The most important are malaria, dengue fever, and chikungunya fever. Vectors play a very crucial role in the transmission of mosquito-borne diseases and protective measures serve as one of the best strategies for the prevention of these diseases. A wide variety of personal protective measures like mosquito nets, screening, repellents, vaporizers and anti-mosquito coils serve this purpose [2]. In India every year there are millions of cases of malaria. Andhra Pradesh is endemic for malaria and other mosquito-borne diseases. Anopheles, Aedes and Culex mosquitoes which transmit these vector-borne diseases are widely prevalent in Andhra Pradesh. Female *Anopheles* mosquitoes transmit malaria, *Aedes aegypti* and some other species of mosquito transmit dengue fever, while *Culex mosquitoes* have been incriminated for the transmission of lymphatic filariasis [3,4]. Therefore, for the effective control of the diseases transmitted by mosquitoes, efforts have been consistently made to educate the community about the danger of mosquito bites [5,4].

For the control of mosquito-transmitted diseases, the Government of India started The National Malaria Control Programme in 1952 and it was renamed as National Vector Borne Disease Control Programme in 2003. Studies conducted in tropical countries have found that human knowledge, attitude and practice of various methods of personal and household protection against mosquito bites vary in different communities [6-10,4]. To prevent mosquito bites different personal protective measures are suggested. They are mosquito nets, screening, repellents, vaporizers and anti-mosquito coils. Under the National Vector Borne Control programme, the Government has introduced Insecticide Treated Nets (ITN) for the community. ITNs are distributed under social marketing in our country [4]. The use of ITN can be very effective against vector-borne diseases, especially malaria [11]. One of the important components of Vector borne

disease control programme is to impart awareness about mosquito bite prevention in the general community. The present community-based study was conducted to assess the awareness and practices of mosquito bite prevention methods amongst households in an urban slum area of South India [4].

2. MATERIALS AND METHODS

The present community-based study was conducted in the Guntur district of Andhra Pradesh. All households of Urban Health Training Center, Shrinavasrao Thota which is the urban catchment area of the Department of Community Medicine, Katuri Medical College, Guntur were selected for the study. Thus 341 families were selected to represent the study area [4]. It was a cross-sectional study. Door-to-door visit was conducted to visit all households. One family member of the household who was present in the house at the time of the visit was included in the study. The study period was from April to June 2010. The pre-designed and pre-tested proforma was used to collect the data [4]. The questionnaire consisted of questions regarding information on various aspects of mosquito bites, breeding places of mosquitoes, measures of prevention of mosquito bites, and diseases transmitted by mosquito bites. The permission to conduct the study was taken from the college's ethical committee. Informed consent was taken before the interview of the study subjects. The collected data was analyzed in Microsoft Excel [4].

3. RESULTS

341 houses were visited for the study. There were 154 males and 187 females who were included in the study. (Table 1) shows the demographic profile of the study population. (Table 2) shows the various aspects of knowledge of mosquito breeding and knowledge regarding diseases transmitted by mosquito bites. 91.50% of the study participants had knowledge about the breeding places of mosquitoes. 22.29% of the study population still had myths that garbage was the breeding place for mosquitoes [4]. 70.09% of the study population had knowledge that mosquito bite is the cause of malaria but only 33.72% of the study population knew that dengue, and chikungunya were transmitted by mosquitoes. Almost 90% of study participants were using one or other personal protective measures against mosquito bites [4]. Multiple responses were given by the study participants. Among them, the commonest method used by the study participants was mosquito coil (52.20) followed by the use of mosquito net (33.14%). 10.85% of the study participants were relying on traditional methods like burning neem leaves (Table 3) [4]. When the study subjects were asked where they were getting information about mosquito bite prevention the majority said from television (71.53%). Other sources were newspapers in 28.35% and IEC materials displayed in health centres in 21.28% of study subjects [4].

4. DISCUSSION

The knowledge about mosquito breeding places in 91.50% of study subjects shows the impact of effective IEC by the government. But Sharma SK et al. [12]

in their study in Madhya Pradesh found that the majority of their study subjects did not have knowledge about mosquito breeding places. The present study showed better awareness amongst the population probably due to good IEC activities in the state [4]. But still, 22.29% of study subjects consider garbage as the breeding place for mosquitoes. Almost 70.09% of the study population had knowledge that mosquito bite causes malaria but only 33.72% of the study population knew that dengue and chikungunya were transmitted by mosquitoes which diseases are increasing in India [4]. Surendren SN [6] in their study in Srilanka found that 71% of study participants were able to name at least one disease transmitted by mosquitoes. Tyagi P [13] in their study from New Delhi observed that 100% of study participants were aware that mosquito bites transmit malaria. In the present study, it was found that 90% of study participants were using one or other personal protective measures against mosquito bites. Surendran SN [6,4] in their study in Sri Lanka found that 96% of study participants were using one or other personal protective measures against mosquito bites, and Babu BV et al. [7] in his study from Orissa found that 99% of urban households; 84% of rural households were using at least one measure against mosquito bites. Snehlatha KS [10] in her study from Pondicherry observed that 99% and 73% of urban and rural respondents respectively were found to use some personal protection against mosquito bites [4]. Panda R et al. [9] in their study from Madhya Pradesh observed that about 55% of study participants were not using any protective measures. The 9% of study subjects who were using protective measures against mosquito bites were found to use various methods like mosquito coil, repellent, mosquito net and traditional Neem leaf burning [4]. They were found to use multiple methods at the same time. In them, the most commonly used method was the mosquito coil (52.20%) followed by using bed net (33.14%.). Snehlatha KS et al. [10] in their study from Pondicherry found mosquito coil as the most common method for prevention against mosquito bites. Babu BV et al 4 in their study from Orissa observed that 76% of the household were using untreated bed nets [4]. In the present study, Bed Net was used by only 33.14% of study subjects but none of the study subjects were using insecticide- treated bed-net (ITN). The awareness about the use of ITN was found poor among the study subjects. Babu BV et al. [7] in their study from Orissa found similar results [4]. It was observed that Television was the main source of awareness for the community followed by newspapers, radio, friends and advertisements. It was disappointing to note that doctor or health staff was not mentioned as the source of knowledge which are coming in contact with people in day-to-day life [4].

Table 1. Demographic profile of study population [4]

Sex	Study subjects (n=341)	Literacy	No	Mean Age
Male	154	Literate	137	38.6
		Illiterate	17	
Female	187	Literate	156	35.2
		Illiterate	31	

Table 2. Knowledge and myths about mosquito and disease transmission [4]

Knowledge	Male (n=154)	Female (n=187)	Total (n=341)
Knowledge about breeding places for mosquito	138(89.61%)	174(93.05%)	312(91.50%)
Garbage is the mosquito breeding site	44(28.57%)	32(17.11%)	76(22.29%)
Knowledge that malaria is caused by mosquito bite	102(66.23%)	137(73.26%)	239(70.09%)
Knowledge that dengue and chikungunya are transmitted by mosquito	51(33.12%)	64(34.22%)	115(33.72%)

Table 3. Protective practices against mosquito bites in study subjects using protective measures [4]

Practices*	No(%)
Mosquito net	113(33.14%)
Mosquito coil	178(52.20%)
Repellent	54(15.84%)
Mosquito killing by racket	36(10.56%)
Traditional way like burning Neem leaves	37(10.85%)

**Multiple responses*

5. CONCLUSION

The study found that knowledge about the causes of malaria and mosquito breeding places was satisfactory in study subjects, but some myths were still prevalent. People should be made aware that mosquito bite causes other diseases also. The cases of Chikungunya fever and dengue fever are increasing in India which requires urgent attention [4]. Insecticide-treated bed-net is a good weapon to fight against mosquito-borne disease and strong social or commercial marketing of these products can definitely increase the acceptance.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Rabindra Hazarika, Sonali Sadhukhan. Knowledge, awareness, practice and preventive method against mosquito borne diseases in Tezpur, Assam, Northeast India. Int J Mosq Res 2024;11(1):125- 128. DOI: https://doi.org/10.22271/23487941.2024.v11.i1b.754
2. Koduri VN, Kusneniwar GN. Awareness about mosquito borne diseases and practice about preventive methods against mosquito bite in rural field practice area of a tertiary care teaching institute, Telangana State. J Med Sci Clin Res. 2018;6:512-8.
3. Park K. Park's Textbook of Preventive and Social Medicine; Bhanot Publication, 20th Edition p-672.
4. Yerpude PN, Jogdand KS, Jogdand M. A study on awareness and practice about preventive methods against mosquito bite among households in an urban slum area of South India. Int J Recent Trends Sci Technol. 2013;8(2):69-71.
5. Heyneman, D. Medical parasitology. In: Medical microbiology, Brooks GF, Butel JS, Morse SA. (eds.). 23rd Edn, McGraw Hill, Boston. 2004;661-701.
6. Surendran SN, Kajatheepan A; Perception and personal protective measures toward mosquito bites by communities in Jaffna District, northern Sri Lanka; J Am Mosq Control Assoc. 2007 Jun;23(2):182-6.
7. Babu BV, Mishra S, Mishra S, Swain BK. Personal- protection measures against mosquitoes: A study of practices and costs in a district, in the Indian state of Orissa, where malaria and lymphatic filariasis are co-endemic. Ann Trop Med Parasitol. 2007 Oct;101(7):601- 9.
8. Ziba C, Slutsker L, Chitsulo L, Steketee RW, Use of malaria prevention measures in Malawian households. Trop Med Parasitol. 1994 Mar;45(1):

70-3.
9. Panda R, Kanhekar LJ, Jain DC, Knowledge, attitude and practice towards malaria in rural tribal communities of south Bastar district of Madhya Pradesh. J Commun Dis. 2000 Sep; 32(3): 222-7.
10. Snehalatha KS, Ramaiah KD, Vijay Kumar KN, Das PK. The mosquito problem and type and costs of personal protection measures used in rural and urban communities in Pondicherry region, South India. Acta Trop. 2003 Sep;88(1):3-9.
11. Lengeler C. Insecticide treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev. 2000;2:CD000363.
12. Sharma SK, Jalees S, Kumar K, Rahman SJ. Knowledge, attitude and beliefs about malaria in a tribal area of Bastar district (Madhya Pradesh); Indian J Public Health. 1993 Oct Dec;37(4):129-32.
13. Tyagi P, Roy A, Malhotra MS, Knowledge, awareness and practices towards malaria in communities of rural, semi-rural and bordering areas of east Delhi (India); J Vect Borne Dis. March 2005;42:30–35.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
International Journal of Recent Trends in Science and Technology, 8(2): 69-71, 2013.
Available:https://statperson.com/Journal/ScienceAndTechnology/Abstract_8_2_2.php

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1344

Chapter 13
Print ISBN: 978-81-976653-0-1, eBook ISBN: 978-81-976653-1-8

Policy Impact Divergence: Multiple Model Regression Analysis of Ghana's 'Free' Maternal Health Care Policy

John Azaare [a*], Kasim Abdulai [b] and Robert Bagngmen Bio [c]

DOI: https://doi.org/10.9734/bpi/dhrni/v1/1262

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1262

ABSTRACT

Background: In July 2008, Ghana introduced a 'free' maternal health care policy (FMHCP) through the National Health Insurance Scheme (NHIS) to provide comprehensive antenatal, delivery and post-natal care services to mothers and their newborns. Although the 'free' policy was originally targeting equity in access to maternal health care, critics observed that the 'free' policy made no plan of responsiveness and quality of care for the unborn and the newborn.
Methods: In a series of analyses, we evaluated the FMHCP impact on maternal healthcare utilization since the policy inception and then estimated the percentage point differences of stillbirth and early neonatal mortality among mothers who benefitted from the policy versus their counterparts who did not.
The study used two rounds of historical data from the Ghana Demographic and Health Survey (GDHS, 2008–2014) and constructed the exposure variable of the FMHCP using mothers' national health insurance status as a proxy variable and another group of mothers who did not subscribe to the 'free' policy. We then generated the propensity scores of the two groups, ex-post, and matched them to determine the impact of the 'free' policy as an intervention on antenatal care uptake and facility-level delivery utilization, using probit and logit models. Our analysis further constructed binary outcomes of stillbirth and perinatal mortality from the under-five mortality data of Ghana's DHS data sets. We applied sample weighting across all analyses to account for clustering and stratification due to the complex design nature of DHS design. All regression analysis accounted for

[a] *Department of Health Service, Policy Planning, Management and Economics, School of Public Health, University for Development Studies, Tamale, Ghana.*
[b] *Department of Clinical Nutrition and Dietetics, Translational Nutrition Research Group, University of Cape Coast, Cape Coast, Ghana.*
[c] *College of Health and Well-Being, Kintampo, Ghana.*
**Corresponding author: E-mail: jazaare@uds.edu.gh;*

confounding variables using maternal individual characteristics deemed statistically significant, alpha value set at $p < 0.005$.
Results: We found antenatal care uptake and facility level delivery increased markedly by 8 and 13 percentage points differences and these were statistically significant; observed coef., 0.08; CI: 95% [0.06–0.10]; $p < 0.001$ and 0.13; CI: 95% [0.11–0.15], $p < 0.001$, respectively. Pregnant women were 1.97 times more likely to make 4+ antenatal visits [WHO recommended minimum number of visits at the time] aOR = 1.97; CI: 95% [1.61–2.4]; $p < 0.001$ and 1.28 times more likely to make 8+ antenatal care visits (WHO current recommended minimum number of visits); aOR: 1.28; CI: 95% [1.10-1.49]; $p < 0.001$. The study also found that pregnant women were 1.87 times more likely to give birth in a healthcare facility of any level in Ghana between 2008 and 2014; aOR = 1.87; CI: 95% [1.57–2.23]; $p < 0.001$. Yet, stillbirth and early neonatal mortality were high showing 12 and 13 percentage points differences in the treatment group, compared to the no-treatment group and the differences were statistically significant; $p = 0.005$, respectively.
Conclusions: In equity terms, the 'free' maternal health policy has made significant strides towards maternal healthcare utilization. However, this does not translate to the desired impact of the decrease in stillbirth and early neonatal mortality in its current form in Ghana.

Keywords: Maternal healthcare utilization; antenatal care uptake; facility delivery; impact evaluation; stillbirth; early neonatal mortality.

ABBREVIATIONS

ANC : Antenatal Care
CSD : Cesarean Section Delivery
DHS : Demographic and Health Survey
FMHCP : Free Maternal Health Care Policy
FDU : Facility Delivery Utilization
GDHS : Ghana Demographic and Health Survey
GHS : Ghana Health Service
MOH : Ministry of Health
NHIA : National Health Insurance Authority
NHIS : National Health Insurance Scheme
WHO : World Health Organization

1. BACKGROUND

Despite multiple and concerted health policy and programme interventions particularly in lower- and middle-income countries (LMICs), maternal mortality remains unacceptably high [1]. Globally, it is estimated that 230 million pregnancies occur annually [2,3] leading to an approximated loss of 800 women's lives each day due to pregnancy or childbirth complications [4,5]. As of 2017, global maternal mortality stood at 211 per 100,000 live births and although this represents a 38% drop since the last 2 decades, it translates to a paltry 2.9% decline per annum which is slower than necessary to meet the Sustainable Development Goal 3 (SDG) target of 70 per 100,000 live births [5,6]. Maternal

mortality is a major public health problem in LMICs and thus, serves as one of the key indicators of a country's standard of living and health care quality [7].

In sub-Saharan Africa, 1 in 38 pregnancies end in mortality compared to 1 in 4,300 pregnancies in Europe and Central Asia [2,5,8,9]. Although maternal mortality has declined significantly in Ghana in the last 2 decades, moving from 740 to 319 per 100,000 live births between 1990 and 2015, the rate of decline is also inadequate to achieve country-level targets [10-12]. Nevertheless, the causes of most maternal deaths in LMICs such as Ghana are preventable or treatable, given pregnancy processes are largely physiological, [13].

Studies have established that quality antenatal care (ANC) and facility-level delivery services provided by trained health personnel impact positively on maternal healthcare outcomes [14-16], yet recent literature in sub-Saharan Africa shows that nearly half of all childbirth occur at home with no support from the services of trained health personnel [10,17,18,6]. In Ethiopia for example, while experienced birth attendants provided ANC for up to 71% of pregnant women, only 16% of pregnant women give birth under trained healthcare personnel supervision [19,20]. Likewise, despite significant improvement in maternal health care delivery in Ghana, only 56% percent of pregnant women give birth under skilled supervision as of 2017 [17,21,22].

Indeed, the World Health Organization (WHO) observed that just around 60% of pregnant women in LMICs have access to expert delivery services compared to 99% of pregnant women in high-income countries, thus requiring deliberate and concerted efforts from LMICs [5,8,12,6].

In time past, Ghana implemented full-cost recovery, popularly called "cash and carry' between 1985 to May 1998, and later antenatal care fee exemption from June 1998 to August 2003 and subsequently, childbirth fee exemption policy from September 2003 to March 2005 (for selected regions; Northern, Upper East, Upper West and Central) and later expanded from 2005 to 2007 [23-25,6]. To address funding constraints, the fee exemption policy was scrapped in 2007 and pregnant women enrolled freely unto the then newly operationalized National Health Insurance Scheme (NHIS) [24,26,27,6] without premium payment, so-called, 'free' maternal health care policy (FMHCP).

As part of the FMHCP, pregnant women who sought maternal health care services at accredited health facilities are automatically registered with the scheme (over a period ending 3 months after childbirth) to receive free comprehensive services including antenatal care, pregnancy-related emergency care, normal delivery care, caesarian section delivery and post-natal care to the mother and the newborn [25,26,6]. Since the 'free' policy implementation, copious studies have examined the impact of fee exemption policies, especially the delivery care fee exemption [27-29] although the evidence suggests that fee exemption for maternal health care was associated with increased uptake of skilled birth care among the poor [29] most of the existing were conducted in selected regions and districts. On the contrary, studies on the impact of the 'free' maternal health care policy following its integration into the NHIS are limited.

While attempts have been made to review, clinical records of 21 hospitals and found an increase in out-patient attendance among pregnant women [30,6] not much has been reported on the impact of the policy on facility delivery utilization, thus, our analysis examined the 'free' impact on antenatal care visits and facility level delivery utilization and further conducted rigorous statistical analysis of the impact of the policy on mortality outcomes i.e., stillbirth and early neonatal mortality as earlier published [28,31] but also reporting judiciously on equity of access to maternal health care [32]. Therefore, this chapter seeks to show equity policy impact and divergence reference to the two studies, and relative to antenatal care uptake, facility delivery utilization, stillbirth outcome and early neonatal mortality in Ghana, to draw lessons to inform policy and practice.

2. METHODS

2.1 Study Design

This study adopted a retrospective design using nationally representative Ghana Demographic and Health Survey (GDHS) (2008–2014), and isolated two groups of women who benefited from the FMHCP as the treatment group and those who did not benefit from the 'free' policy as the no-treatment group by merging the two rounds of the repeated cross-sectional survey, pre- and post-policy [6]. We defined antenatal care uptake as pregnant women receiving antenatal care at least four times or more considered standard requirement by WHO at the time [14,25] and also defined facility-level delivery utilization to include all childbirths conducted in a health care facility of any level in Ghana between 2008 and 2014. At the time of conducting this analysis, the Ghana 2014 DHS was the current available DHS data set considered wide and nationally representative with comparable variables since the 'free' maternal health care policy inception in 2008. The most recent DHS (Ghana: Standard, 2022) was published in May 2023. However, this report and the data it contains were unavailable at the time this manuscript was created and submitted.

2.2 Data Source

The study used two rounds of repeated cross-sectional surveys of the Ghana DHS 2008 and 2014 extracted from the website of Measure DHS upon completion of an online application process [6]. The DHS data sets were considered appropriate as they offered baseline and end-line data on the FMCHP's implementation and allowed for comparison. Variables *m14* and *m15* from the original data sets were used to construct two outcomes of interest: ante-natal care uptake and facility-level delivery utilization, respectively.

2.3 Exposure Variable

In practice, pregnant women have access to the FMHCP through free registration with the NHIS. Hence, women registered under the scheme were used as proxy variables and classified as having subscribed to the FMHCP and a binary

variable of '1' and '0' constructed to represent benefiting from the 'free' policy or otherwise, respectively [6].

2.4 Dependent Variable

Multiple dependent variables were considered; antenatal care uptake, facility-level delivery utilization, stillbirth and perinatal death. All dependent variables are analyzed and reported individually.

2.5 Independent Covariate

Drawing on Mosley and Chen's conceptual framework (Fig. 1) for studying child survival rates and other literature [22], maternal age, area of residence, parity, abortion history, employment status, education, wealth index, and region were adjusted for as independent covariates for precision. All models were built using a stepwise approach to determine relevant independent covariates based on their statistical significance.

2.6 Statistical Analysis

Using STATA version 16, we constructed a binary outcome of '1' representing 'four or more antenatal care uptake' and '0' representing 'three to zero antenatal care uptake' as no-antenatal care uptake'. We further constructed another set of binary outcomes for facility delivery utilization, thus, '1' represented 'facility-level delivery utilization' and '0' for otherwise. The bivariate analysis of independent covariates (Table 1) was unadjusted. Results with alpha values < 0.05 were considered statistically significant and then adjusted for in the logistics regression analysis of which the results of association were reported in adjusted odd ratios (aOR) [6]. We then estimated the impact of the FMHCP as an intervention on ANC uptake and facility-level delivery utilization using the propensity scores, generated ex-post between the two groups with probit and logit models leaving the results in coefficients of determination, 95% confident interval and a statistical significance level of $p < 0.05$.

2.7 Sensitivity Analysis

We adjusted for the complex design of the DHS data sets by applying sample weighting using the primary sampling units (v021) and rural/urban area of residence (v022), hence selected *v005* and divided by 1,000,000 in Stata to cater for 6 decimal places (usually not accounted for in STATA version of the data sets). We then prefixed all Stata commands with *'svy'* afterwards using Taylor linearization for reduced standard error. The models were repeated in a negative binomial regression with robust standard error to test for sensitivity and over-dispersion. Also, box plots (Fig. 2) and Kernel density curve graphs (Fig. 3) were plotted to check for overlap and common support in the matching method [6]. The study checked for homogeneity between the two groups using standardized bias with t-test statistics (Fig. 4) [6].

2.8 Ethical Considerations

This study received ethical clearance from Ghana Health Service with registration number GHS-ERC 002/04/19 and also received an access note from the DHS programme to use the Ghana DHS data sets.

3. RESULTS

3.1 Descriptive Statistics

Of the study participants (n=8876), mean maternal ages were 30 and 31 years for 2008 and 2014, respectively. Mean parity and mean antenatal care were 4 and 6, respectively for both rounds of DHS data sets (Table 2) and the differences were statistically significant, $p < 0.05$ (Table 1) [6].

Associated factors of four and eight pluses antenatal care visits, facility delivery utilization and the 'free' maternal health care policy

Pregnant women were 1.97 times more likely to make four plus antenatal care visits (Table 3a), aOR: 1.97; CI: 95% [1.61–2.4]; $p = 0.001$ and 1.28 times more likely to make eight plus antenatal care visits (Table 3b), aOR: 1.28; CI: 95% [1.10-1.49]; $p < 0.001$. Antenatal care uptake increased with increasing maternal age; aOR = 1.05; 95% CI: [1.03–1.07]; $p = 0.05$. Women with employment and women with a secondary level of education were more likely to visit antenatal clinics compared to women with no employment and women with no formal education; aOR = 1.46; 95% CI: [1.16-1.84]; $p < 0.001$ and aOR = 1.59; 95% CI: [1.23–2.06]; $p < 0.001$. Women in Greater Accra; aOR = 0.54; CI: 95% [0.31–0.93]; $p = 0.028$, Volta region; aOR = 0.52; CI: 95% [0.32–0.83]; $p = 0.007$ and Eastern region; aOR = 0.44; CI: 95% [0.29–0.68]; $p = 0.001$ were less likely to make four plus antenatal care visits compared to women in the reference (Western) region. Similarly in Table 4, pregnant women were 1.87 times more likely to deliver in a healthcare facility in the FMHCP group compared to those who did not subscribe to the 'free' policy; aOR = 1.87; CI: 95% [1.57–2.23]; $p < 0.001$.

Maternal age, aOR = 1.03; CI: 95% [1.01–1.05]; $p < 0.001$, secondary education, aOR = 1.78; CI: 95% [1.40–2.26], $p < 0.001$, history of abortion aOR = 1.31; CI: 95% [1.07– 1.60]; $p = 0.009$, and 4 + antenatal care visits; aOR = 3.2; CI: 95% [2.61–3.92]; $p < 0.001$ predicted facility level delivery utilization and these were statistically significant in association [6].

Pregnant women in the Upper East region, aOR = 2.96; CI: 95% [1.75–4.98]; $p < 0.001$ and Brong-Ahafo region, aOR = 1.60; CI: 95% [1.00-2.56]; $p = 0.049$ regions were more likely to give birth in a health care facility compared to pregnant women in the reference region.

3.2 Percentage Points Increase in Antenatal Care Uptake, Facility Level Delivery Utilization, Stillbirth and Perinatal Mortality

Antenatal care uptake and facility delivery utilization increased by 8 and 13 percentage points, respectively, observed coefficient; 0.08; CI: 95% [0.06–0.10]; $p < 0.001$ and 0.13; CI: 95% [0.11–0.15]; $p < 0.001$, and these were statistically significant (Table 5) [6]. Unexpectedly, stillbirth and perinatal mortality (stillbirth and early neonatal mortality) also increased among pregnant women who benefitted from the 'free' policy by 12 and 13 percentage points [31].

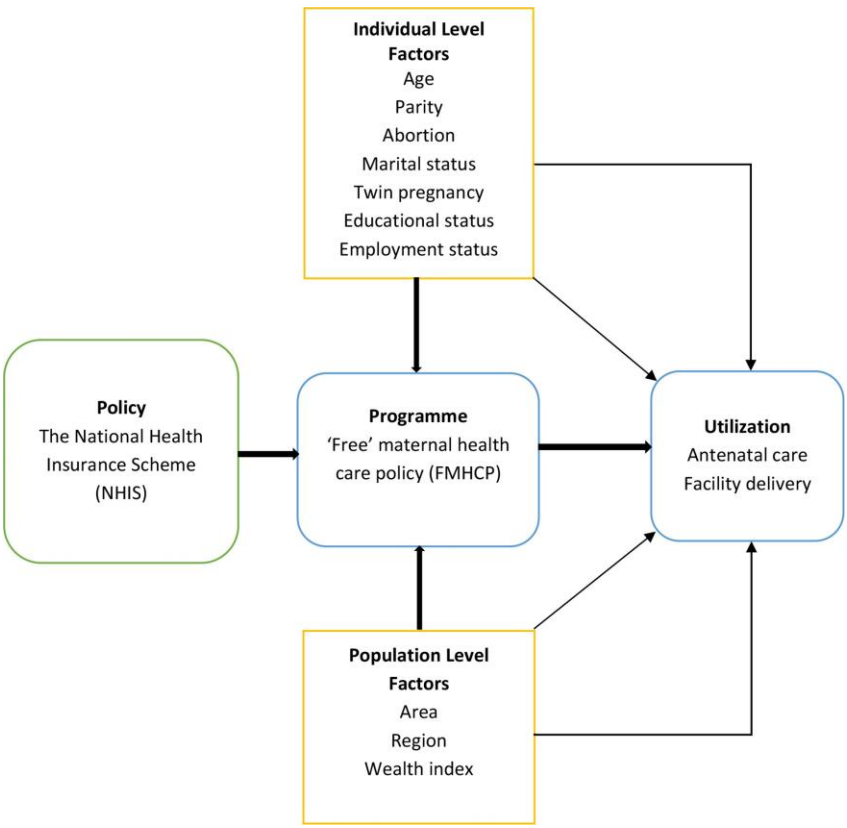


Fig. 1. Factors influencing maternal health care utilization. (adapted from Azaare et al., 2020)

Table 1. Bivariate analysis of antenatal care uptake, facility delivery utilization and independent covariates

Variable	Antenatal Care Uptake			Facility Delivery Utilization		
	uOR	**CI: (95%)**	***P*-value**	**uOR**	**CI: 95%**	***P*-value**
No_FMHCP	1			1		
FMHCP	2.69	(2.25–3.21)	0.001***	2.37	(2.03–2.77)	0.001***
Age	1.01	(1.00-1.03)	0.006*	1.00	(0.99-1.00)	0.996
Parity	0.87	(0.84–0.90)	0.001***	0.81	(0.78–0.83)	0.001***
History of abortion						
No history of abortion	1			1		
History of abortion	1.59	(1.26–2.01)	0.001***	1.93	(1.62–2.31)	0.001***
delivery place				1		
Home delivery	1			6.03	(4.89–7.44)	0.001***
Facility delivery	1.16	(1.14–1.19)	0.001***			
Area of residence						
Urban	1			1		
Rural	0.34	(0.27–0.44)	0.001***	0.14	(0.11–0.18)	0.001***
Employment						
Unemployed	1			1		
Employed	1.25	(1.01–1.55)	0.035*	0.74	(0.60–0.91)	0.005*
Education						
No education	1			1		
Primary	1.18	(0.92–1.51)	0.185	2.01	(1.63–2.49)	0.001***
Secondary	3.24	(2.50–4.21)	0.001***	5.69	(4.56–7.09)	0.001***
Tertiary	26.2	(4.59-150.16)	0.001***	51.6	(12.89–207.4)	0.001***
Marital status						
Unmarried	1			1		
Married	1.28	(0.94–1.75)	0.107	0.64	(0.46–0.87)	0.005*
Liv. tog.	0.92	(0.66–1.28)	0.624	0.65	(0.47–0.89)	0.009*
Widowed	0.85	(0.46–1.60)	0.632	0.39	(0.22–0.69)	0.001**
Divorced	1.06	(0.47–2.36)	0.876	1.21	(0.58–2.53)	0.598
Not liv. tog.	1.07	(0.68–1.68)	0.767	0.75	(0.48–1.19)	0.228
Wealth Index						
Poorest	1			1		
Poorer	1.44	(1.11–1.88)	0.006*	2.14	(1.71–2.69)	0.001***

Variable	Antenatal Care Uptake			Facility Delivery Utilization		
	uOR	**CI: (95%)**	***P*-value**	**uOR**	**CI: 95%**	***P*-value**
Middle	2.01	(1.49–2.71)	0.001***	4.18	(3.21–5.43)	0.001***
Richer	5.14	(3.50–7.54)	0.001***	13.13	(9.60-17.97)	0.001***
Richest	15.0	(8.34–27.2)	0.001***	39.65	(25.70-61.18)	0.001***
Region						
Western	1			1		
Central	0.91	(0.55–1.51)	0.740	0.82	(0.57–1.18)	0.286
G. Accra	1.56	(0.96–2.52)	0.071	4.30	(2.73–6.77)	0.001***
Volta	0.44	(0.28–0.71)	0.001**	0.70	(0.47–1.07)	0.101
Eastern	0.44	(0.29–0.67)	0.001***	0.83	(0.58–1.20)	0.336
Ashanti	1.43	(0.90–2.26)	0.124	1.82	(1.26–2.64)	0.001**
Brong-Ahafo	0.96	(0.58–1.58)	0.880	1.23	(0.81–1.86)	0.321
Northern	0.35	(0.21–0.58)	0.001***	0.20	(0.13–0.33)	0.001***
Upper East	1.13	(0.67–1.93)	0.629	1.00	(0.65–1.56)	0.966
Upper West	1.15	(0.69–1.91)	0.570	0.59	(0.37–0.96)	0.035*

*uOR - unadjusted odd ratio; 1– reference; *p < 0.05; **p = 0.001; ***p < 0.001*

4. DISCUSSION

Our study found that pregnant women made four or more antenatal care visits and were more likely to deliver in a health care facility of any level following the 'free' policy implementation and the differences are statistically significant, $p < 0.001$. Similarly, we found a 1.28 likelihood of eight plus ANC visits in accordance with the WHO current recommendation relative to the 'free' policy (Table 3b). In essence, pregnant women are more likely to utilize antenatal care services and give birth in a health care facility of any level in Ghana relative to the 'free' maternal health care policy implementation.

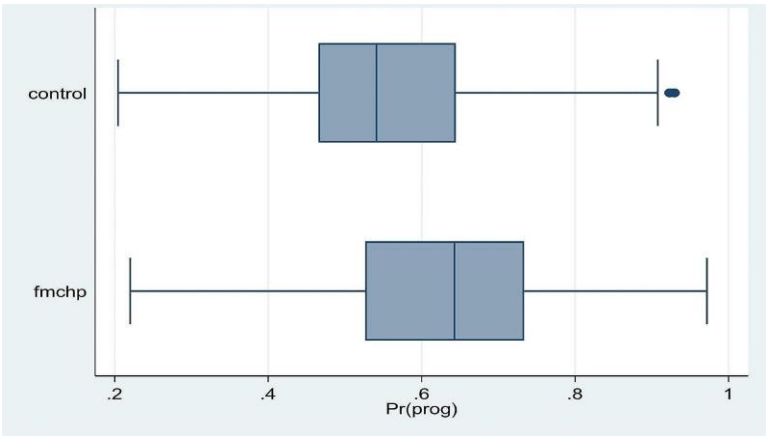


Fig. 2. Fig. Box plot graph comparing the 'free' maternal health care policy and the control group

While the analysis of association showed a stronger correlation between the 'free' policy and uptake of antenatal care compared to facility delivery utilization, the policy impact estimation found an eight percentage point difference in favor of facility-level delivery utilization. There are two possibilities that explain this scenario. First, pregnant women are more likely to come for antenatal care services during pregnancy but they give birth in a health facility only when complications accompany the pregnancy. This probably explains the high rate of stillbirth and early neonatal mortality among subscribers of the 'free' policy as earlier reported [28,6]. Secondly, facility delivery utilization is perhaps benefiting more from the 'free' policy impact relative to unapproved charges associated with facility delivery services uptake due to NHIS claims payment delays as reported in the earlier study [29].

While lessons could be drawn from the current study, the results should be linked to specific elements of ANC uptake to determine the clinical benefits of ANC uptake in Ghana as argued by Hodgin and D'Agostino [30,33].

Our study further found that pregnant women were more likely to deliver in a health care facility in the Upper East region, compared to other regions in Ghana

and this is consistent with the findings of the State of the Nation's Health' report by the University of Ghana School of Public Health [34]. It should be noted that Ghana initiated a primary health care concept in the early 2000s known as the Community-Based Health Planning Services (CHPS) a nationwide national health reform programme aimed at bringing health care to the doorsteps of local communities, an equity policy intervention. The CHPS concept was piloted in the Upper Esat region and is well accepted in that region, thus probably playing a crucial role in increasing access to maternal health care despite the deprived nature of the region. Secondly, being one of the poorest regions of Ghana [35], pregnant women, perhaps, and rationally so, have a higher propensity to subscribe to and use the 'free' policy compared to pregnant women in other regions [6].

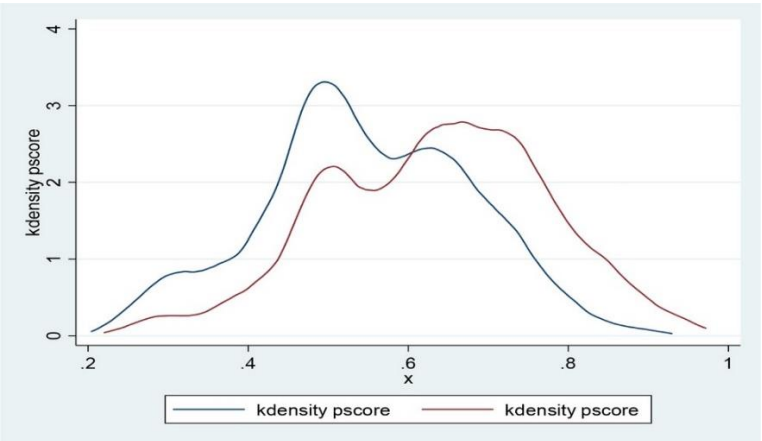


Fig. 3. Kernel density plot showing common support for comparison between the intervention and control groups

Pregnant women in the Greater Accra, Volta and Eastern regions were less likely to make ANC visits and although the reasons are unclear within the scope of the current analysis, the odds of pregnant women paying out-of-pocket in the Greater Accra and Eastern regions are probably higher due to the availability and perceived quality of care in the private health care sector as well as the financial wherewithal [36,37], nevertheless, the current finding is a piece of useful evidence in setting the stage for increasing investment in maternal health care in Ghana to support the realization of the global targets of 70 per 100,000 live birth maternal mortality rate by 2030. The findings of the current study have implications for policy and practice yet outline Ghana's potential to achieve WHO current recommendations of eight minimum antenatal care visits required per pregnancy to guarantee adequate pre-natal observation [14,15, 6].

Further, a natural expectation is that as the 'free' policy brings care to pregnant women, this should impact positively leading to a decrease in stillbirth rates and neonatal mortality rates, however, this is where the 'free' policy diverges in its impact and outcome, thus achieving equity in access, yet not achieving a desired

decline in stillbirth and early neonatal mortality. First and foremost, our key recommendation is for the government of Ghana to deliberately train expert personnel such as neonatal care nurses to support the efforts of midwives who are already in short supply and stretched in Ghana. This is a call for an increase in investments such as budgetary allocation to the Ministry of Health (MOH) to up effective and funded demand for the health workforce, particularly midwives, pediatricians and neonatologists to ensure that newborns get the level of care required at all material moment to safe life. Suffice it to note that in recent times, government budgetary allocation to the MOH is declining in Ghana, from 7.6% in 2022 to 6.7% in 2023, far less than the 15% target by the Abuja declaration towards Universal Health Coverage (UHC). The current evidence beckons a reversal of the declining trend in budgetary allocation forthwith. It is also imperative to examine the quality of care delivered during antenatal care and actual delivery services, and perhaps improve the aspects that are necessary such as adequately serving appropriate supplemental medications such as folic acid and ferrous to pregnant women and ensuring clinical staff have the means competencies to initiate effective resuscitation systems post-delivery across district hospitals in Ghana.

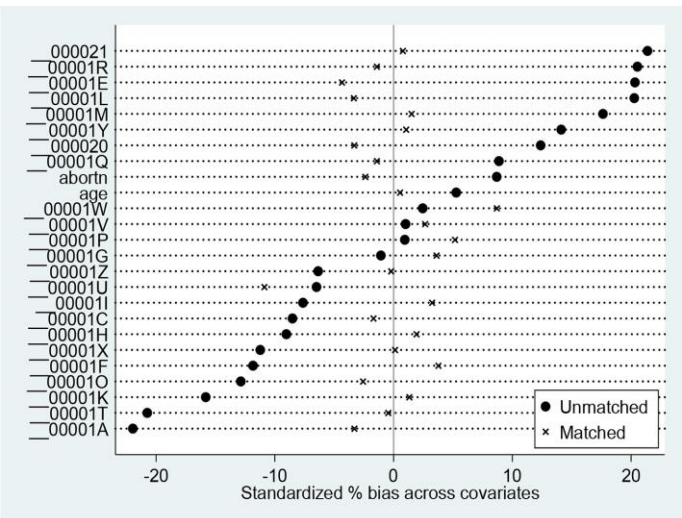


Fig. 4. Standardized test of bias showing the matched characteristics around or close to line zero

Table 2. Descriptive statistics

Variable	Observation	2008		2014	
		N	Mean	N	Mean
Maternal Age	8,876	2,992	30	5,884	31
Antenatal Care	6,360	2,088	6	4,272	6
Parity	8,876	2,992	4	5,884	4

Table 3a. Multivariate analysis of association between the 'free' maternal health care policy and four plus antenatal care visits

Variable	Multiple logistic regression with linearized std. error			Poisson regression with linearized std. error			Negative binomial regression With linearized std. error		
	aOR	**(CI: 95%)**	***P*-Value**	**aPR**	**(CI: 95%)**	***P*-Value**	**aPR**	**(CI: 95%)**	***P*-value**
No_FMHCP	1			1			1		
FMHCP	1.97	(1.61–2.41)	0.001***	0.09	(0.06–0.11)	0.001***	0.09	(0.07–0.11)	0.001***
Age	1.05	(1.03–1.07)	0.001***	0.01	(0.003–0.01)	0.001***	0.01	(0.004–0.01)	0.001***
Parity	0.84	(0.79–0.90)	0.001***	-0.02	(-0.02-0.01)	0.001***	-0.02	(-0.03 -0.01)	0.001***
Abortion									
No history of abortion	1			1			1		
History of abortion	1.13	(0.88–1.46)	0.312	0.01	(-0.01-0.03)	0.305	0.02	(-0.003–0.04)	0.094
Delivery place									
Home delivery	1			1			1		
Facility delivery	3.20	(2.61–3.92)	0.001***	0.22	(0.18–0.26)	0.001***	0.22	(0.18–0.25)	0.001***
Area of residence									
Urban	1			1			1		
Rural	1.03	(0.79–1.35)	0.774	0.01	(-0.02-0.04)	0.706	-0.002	(-0.02–0.023)	0.881
Employment									
Unemployed	1			1			1		
Employed	1.46	(1.16–1.84)	0.001***	0.04	(0.007–0.07)	0.016*	0.03	(0.005 − 0.06)	0.023*
Education									
No education	1			1			1		
Primary	1.02	(0.80–1.28)	0.867	-0.003	(-0.04-0.04)	0.868	0.002	(-0.03–0.03)	0.925
Secondary	1.59	(1.23–2.06)	0.001***	0.047	(0.01–0.08)	0.010*	0.04	(0.01–0.06)	0.013*
Tertiary	3.69	(0.63–21.3)	0.144	0.038	(-0.002-0.07)	0.065	0.03	(-0.01- 0.06)	0.061
Marital status									
Not married	1			1			1		
Married	1.38	(0.96–1.97)	0.077	0.027	(-0.02-0.07)	0.249	0.05	(0.01–0.09)	0.028*
Liv. together	1.07	(0.73–1.56)	0.723	-0.001	(-0.05-0.05)	0.977	0.01	(-0.03–0.06)	0.624
Widowed	1.02	(0.53–1.97)	0.936	-0.001	(-0.10-0.09)	0.978	0.01	(-0.08–0.10)	0.847
Divorced	1.14	(0.50–2.59)	0.748	0.01	(-0.10-0.12)	0.880	0.01	(-0.08–0.09)	0.857
Not liv. together	1.25	(0.78–1.99)	0.343	0.02	(-0.04-0.08)	0.563	0.01	(-0.05–0.08)	0.668
Wealth index									
Poorest	1			1			1		

Variable	Multiple logistic regression with linearized std. error			Poisson regression with linearized std. error			Negative binomial regression With linearized std. error		
	aOR	**(CI: 95%)**	***P*-Value**	**aPR**	**(CI: 95%)**	***P*-Value**	**aPR**	**(CI: 95%)**	***P*-value**
Poorer	1.19	(0.92–1.53)	0.164	0.05	(-0.004-0.10)	0.067	0.04	(-0.001- 0.07)	0.056*
Middle	1.25	(0.92–1.71)	0.150	0.06	(0.01–0.12)	0.029*	0.06	(0.01–0.09)	0.006*
Richer	2.23	(1.42–3.49)	0.001***	0.09	(0.04–0.15)	0.001**	0.09	(0.05–0.13)	0.001***
Richest	4.72	(2.33–9.56)	0.001***	0.10	(0.04–0.16)	0.001**	0.08	(0.03–0.12)	0.001**
Region									
Western	1			1			1		
Central	1.16	(0.72–1.84)	0.532	0.02	(-0.03- 0.07)	0.500	0.02	(-0.02–0.05)	0.398
G. Accra	0.54	(0.31–0.93)	0.028*	-0.04	(-0.08–0.01)	0.098	-0.02	(-0.05–0.02)	0.361
Volta	0.52	(0.32–0.83)	0.007*	-0.10	(-0.17- -0.02)	0.006	-0.09	(-0.15 - -0.04)	0.001***
Eastern	0.44	(0.29–0.68)	0.001***	-0.12	(-0.17- -0.06)	0.001***	-0.11	(-0.16 - -0.06)	0.001***
Ashanti	1.10	(0.67–1.79)	0.701	0.01	(-0.04- -0.05)	0.757	0.01	(-0.02–0.05)	0.506
Brong-Ahafo	1.03	(0.63–1.69)	0.892	0.004	(-0.05- -0.05)	0.877	0.01	(-0.02–0.05)	0.529
Northern	0.75	(0.47–1.21)	0.249	-0.05	(-0.13- -0.04)	0.253	-0.07	(-0.13 - -0.02)	0.003
Upper East	1.41	(0.80–2.49)	0.232	0.65	(0.002–0.13)	0.045*	0.06	(0.01–0.10)	0.013*
Upper West	1.67	(0.97–2.88)	0.062	0.08	(0.02–0.14)	0.011*	0.07	(0.02- 0.11)	0.005*

*aCoef.– adjusted coefficient; * p < 0.05; **p = 0.001; ***p < 0.001*

Table 3b. Multivariate analysis of the association between the 'free' maternal health care policy and eight plus visits of antenatal care

Variable	Multiple logistic regression with linearized std. error			Poisson regression with linearized std. error			Negative binomial regression With linearized std. error		
	aOR	(CI: 95%)	P-Value	aPR.	(CI: 95%)	P-Value	aPR.	(CI: 95%)	P-value
No_FMHCP	1			1			1		
FMHCP	1.28	(1.10-1.49)	0.001**	1.16	(1.05-1.28)	0.002*	1.16	(1.05-1.28)	0.002*
Age	1.03	(1.01-1.05)	0.001***	1.01	(1.00-1.03)	0.001***	1.01	(1.00-1.03)	0.001***
Parity	0.90	(0.89-1.30)	0.001**	0.94	(0.91-0.97)	0.002*	0.94	(0.91-0.97)	0.002*
Abortion									
No	1			1			1		
Yes	1.08	(0.89-1.30)	0.408	1.04	(0.94-1.16)	0.408	1.04	(0.94-1.16)	0.408
Facility delivery									
No	1			1			1		
Yes	2.41	(1.96-2.97)	0.001***	1.95	(1.65-2.30)	0.001***	1.95	(1.65-2.30)	0.001***
Area of residence									
Urban	1			1			1		
Rural	1.03	(0.82-1.29)	0.776	1.02	(0.89-1.17)	0.741	1.02	(0.89-1.17)	0.741
Employment									
No	1			1			1		
Yes	1.13	(0.92-1.39)	0.229***	1.07	(0.94-1.22)	0.257	1.07	(0.94-1.22)	0.257
Education									
No education	1			1			1		
Primary	1.10	(0.88-1.38)	0.373	1.07	(0.91-1.25)	0.367	1.07	(0.91-1.25)	0.367
Secondary	1.14	(0.92-1.42)	0.216***	1.09	(0.94-1.26)	0.229	1.09	(0.94-1.26)	0.229
Tertiary	1.49	(0.97-2.29)	0.066	1.23	(0.982-1.54)	0.064	1.23	(0.982-1.54)	0.064
Marital status									
Not married	1			1			1		
Married	1.27	(0.95-1.70)	0.097	1.16	(0.96-1.40)	0.104	1.16	(0.96-1.40)	0.104
Liv. together	1.24	(0.90-1.71)	0.182	1.14	(0.93-1.41)	0.194	1.14	(0.93-1.41)	0.194
Widowed	1.49	(0.80-2.79)	0.205	1.29	(0.89-1.88)	0.176	1.29	(0.89-1.88)	0.176
Divorced	0.98	(0.59-1.62)	0.953	1.00	(0.72-1.38)	0.991	1.00	(0.72-1.38)	0.991
Not liv. together	1.06	(0.66-1.68)	0.803	1.04	(0.76-1.40)	0.795	1.04	(0.76-1.40)	0.795
Wealth index									

Variable	Multiple logistic regression with linearized std. error			Poisson regression with linearized std. error			Negative binomial regression With linearized std. error		
	aOR	**(CI: 95%)**	**P-Value**	**aPR.**	**(CI: 95%)**	**P-Value**	**aPR.**	**(CI: 95%)**	**P-value**
Poorest	1			1			1		
Poorer	1.26	(0.97-1.63)	0.076	1.26	(1.02-1.54)	0.026	1.26	(1.02-1.54)	0.026
Middle	1.56	(1.14-2.13)	0.005	1.47	(1.17-1.85)	0.001**	1.47	(1.17-1.85)	0.001**
Richer	2.12	(1.54-2.92)	0.001***	1.77	(1.41-2.22)	0.001***	1.77	(1.41-2.22)	0.001***
Richest	2.84	(1.99-4.05)	0.001***	2.02	(1.58-2.58)	0.001***	2.02	(1.58-2.58)	0.001***
Region									
Western	1			1			1		
Central	0.53	(0.36-0.77)	0.001**	0.71	(0.58-0.86)	0.001**	0.71	(0.58-0.86)	0.001**
G. Accra	0.48	(0.34-0.70)	0.001***	0.68	(0.57-0.81)	0.001***	0.68	(0.57-0.81)	0.001***
Volta	0.39	(0.26-0.57)	0.001***	0.58	(0.47-0.73)	0.001***	0.58	(0.47-0.73)	0.001***
Eastern	0.23	(0.15-0.35)	0.001***	0.41	(0.31-0.53)	0.001***	0.41	(0.31-0.53)	0.001***
Ashanti	0.46	(0.32-1.66)	0.001***	0.66	(0.55-0.79)	0.001***	0.66	(0.55-0.79)	0.001***
Brong-Ahafo	0.47	(0.32-0.70)	0.001***	0.67	(0.54-0.83)	0.001***	0.67	(0.54-0.83)	0.001***
Northern	0.17	(0.10-0.28)	0.001***	0.29	(0.20-0.42)	0.001***	0.29	(0.20-0.42)	0.001***
Upper East	0.38	(0.23-0.63)	0.001***	0.59	(0.42-0.81)	0.001**	0.59	(0.42-0.81)	0.001**
Upper West	0.26	(0.18-0.40)	0.001***	0.44	(0.34-0.56)	0.001***	0.44	(0.34-0.56)	0.001***

*aCoef. – adjusted coefficient; * p < 0.05; **p = 0.001; ***p < 0.001*

Table 4. Multivariate analysis of association between the 'free' maternal health care policy and facility delivery utilization

Variable	Multiple logistic regression with linearized std. error			Poisson regression with linearized std. error			Negative binomial regression with robust std. error		
	aOR	**(CI: 95%)**	***P*-Value**	**aPR**	**(CI: 95%)**	***P*-Value**	**aPR**	**(CI: 95%)**	***P*-value**
No_FMHCP	1			1			1		
FMHCP	1.87	(1.57–2.23)	0.001***	0.14	(0.10–0.18)	0.001***	0.18	(0.14–0.21)	0.001***
Age	1.03	(1.01–1.05)	0.001***	0.01	(0.003–0.01)	0.001***	0.01	(0.004–0.01)	0.001***
Parity	0.87	(0.82–0.93)	0.001***	-0.03	(-0.04- -0.01)	0.001***	-0.04	(-0.05 - -0.02)	0.001***
Abortion									
No history of abortion	1			1			1		
History of abortion	1.31	(1.07–1.60)	0.009*	0.05	(0.01–0.08)	0.007*	0.03	(-0.005–0.06)	0.103
Antenatal care									
0–3 attendance	Ref.			1			1		
4 + attendance	3.20	(2.61–3.92)	0.001***	0.50	(0.39–0.61)	0.001***	0.52	(0.44–0.60)	0.001***
Area of residence									
Urban	1			1			1		
Rural	0.44	(0.34–0.56)	0.001***	-0.17	(-0.22- -0.15)	0.001***	-0.19	(-0.23- 0.15)	0.001***
Employment									
Unemployed	1			1			1		
Employed	0.88	(0.70–1.09)	0.260	-0.04	(-0.07-0.01)	0.094	-0.03	(-0.06 − 0.004)	0.085
Education									
No education	1			1			1		
Primary	1.19	(0.94–1.52)	0.142	0.08	(0.01–0.15)	0.046	0.11	(0.05–0.16)	0.001***
Secondary	1.78	(1.40–2.26)	0.001***	0.14	(0.07–0.20)	0.001***	0.17	(0.12–0.22)	0.001***
Tertiary	3.44	(0.76–15.5)	0.108	0.14	(0.6 − 0.21)	0.001***	0.16	(0.10–0.21)	0.001***
Marital status									
Not married	1			1			1		
Married	0.79	(0.56–1.12)	0.197	-0.05	(-0.11-0.01)	0.099	-0.07	(-0.13- -0.24)	0.005*
Liv. together	0.79	(0.56–1.14)	0.205	-0.04	(-0.10-0.02)	0.202	-0.07	(-0.12- -0.01)	0.016*
Widowed	0.41	(0.19–0.83)	0.014*	-0.22	(-0.40- -0.04)	0.016	-0.17	(-0.32- -0.02)	0.024*
Divorced	1.87	(0.83–4.24)	0.129	0.10	(-0.03-0.24)	0.133	0.03	(-0.08- 0.14)	0.565
Not liv. together	0.79	(0.46–1.36)	0.407	-0.05	(-0.16-0.43)	0.260	-0.12	(-0.21- 0.02)	0.014*
Wealth index									
Poorest	1			1			1		

Variable	Multiple logistic regression with linearized std. error			Poisson regression with linearized std. error			Negative binomial regression with robust std. error		
	aOR	**(CI: 95%)**	***P*-Value**	**aPR**	**(CI: 95%)**	***P*-Value**	**aPR**	**(CI: 95%)**	***P*-value**
Poorer	1.64	(1.34–2.01)	0.001***	0.26	(0.16–0.35)	0.001***	0.20	(0.14–0.27)	0.001***
Middle	2.08	(1.60–2.71)	0.001***	0.35	(0.25–0.46)	0.001***	0.29	(0.22–0.36)	0.001***
Richer	4.20	(2.85–6.17)	0.001***	0.43	(0.33–0.54)	0.001***	0.34	(0.27–0.41)	0.001***
Richest	6.11	(3.59–10.3)	0.001***	0.39	(0.28–0.50)	0.001***	0.31	(0.24–0.38)	0.001***
Region									
Western	1			1			1		
Central	0.87	(0.55–1.37)	0.556	-0.03	(-0.13- 0.06)	0.501	0.03	(-0.04- 0.09)	0.469
G. Accra	1.55	(0.92–2.63)	0.098	0.07	(-0.01-0.15)	0.067	0.08	(0.03–0.14)	0.002*
Volta	1.21	(0.75–1.96)	0.418	0.04	(-0.06-0.16)	0.420	0.04	(-0.02- -0.12)	0.198
Eastern	1.08	(0.70–1.66)	0.707	0.02	(-0.07-0.12)	0.634	0.05	(-0.01- -0.12)	0.110
Ashanti	1.54	(0.99–2.38)	0.052	0.08	(-0.001-0.16)	0.053	0.11	(0.05–0.17)	0.001***
Brong-Ahafo	1.60	(1.00-2.56)	0.049*	0.09	(-0.001-0.19)	0.053	0.13	(0.07–0.19)	0.001***
Northern	0.62	(0.38-1.00)	0.054	-0.25	(-0.43- -0.07)	0.006	-0.21	(-0.03- -0.12)	0.001***
Upper East	2.96	(1.75–4.98)	0.001***	0.34	(0.21–0.46)	0.001***	0.32	(0.24–0.39)	0.001***
Upper West	1.45	(0.86–2.45)	0.165	0.11	(-0.03-0.26)	0.135	0.11	(0.03–0.19)	0.006*

aPR– adjusted Prevalence Ratio; * p < 0.05; *** p < 0.001

Table 5. Impact of the 'free' maternal health care policy on antenatal care uptake and facility delivery utilization; kernel propensity score analysis using logit regression model

Variable	Bootstrapping standard error					
	Antenatal care uptake			Facility delivery utilization		
	ATE	**(CI: 95%)**	***P*-value**	**ATE**	**(CI: 95%)**	***P*-value**
No_FMHCP	**1**			**1**		
FMHCP	0.08	(0.06–0.10)	0.001***	0.13	(0.11–0.15)	0.001***
Age	0.003	(-0.002-0.008)	0.231	0.004	(0.0001–0.008)	0.043*
Abortion						
No	**1**			**1**		
Yes	0.12	(0.04–0.20)	0.004*	0.13	(0.06–0.20)	0.001***
Area of residence						
Urban	**1**			**1**		
Rural	-0.06	(-0.15-0.02)	0.176	-0.09	(-0.17- -0.01)	0.021*
Employment						
No	**1**			**1**		
Yes	-0.12	(-0.21-0.03)	0.008	-0.13	(-0.20 - -06)	0.001***
Education						
No education	**1**			**1**		
Primary	0.03	(-0.06-0.13)	0.486	0.06	(0.21 − 0.13)	0.151
Secondary	0.39	(0.29–0.48)	0.001***	0.41	(0.32–0.48)	0.001***
Tertiary	0.67	(0.44–0.90)	0.001***	0.68	(0.47–0.87)	0.001***
Marital status						
Not married	**1**			**1**		
Married	0.33	(-0.20-0.47)	0.001) ***	0.36	(0.24–0.49)	0.001***
Liv. together	0.15	(o.01-0.29)	0.035*	0.21	(0.08–0.33)	0.001**
Widowed	0.21	(-0.07- -0.49)	0.148	0.22	(-0.04-0.47)	0.103
Divorced	-0.16	(-0.44-0.12)	0.265	-0.16	(-0.42- 0.09)	0.210
Not liv. together	-0.09	(-0.11-0.31)	0.367	0.10	(-0.08- 0.29)	0.290
Wealth index						
Poorest	**1**			**1**		
Poorer	0.16	(0.06–0.26)	0.002*	0.16	(0.07–0.24)	0.001***
Middle	0.32	0.20–0.43)	0.001***	0.31	(0.20–0.41)	0.001***
Richer	0.43	(0.29–0.57)	0.001***	0.42	(0.29–0.54)	0.001***

Variable	**Bootstrapping standard error**					
	Antenatal care uptake			**Facility delivery utilization**		
	ATE	**(CI: 95%)**	***P*-value**	**ATE**	**(CI: 95%)**	***P*-value**
Richest	0.61	(0.44–0.78)	0.001***	0.61	(0.45–0.75)	0.001***
Region						
Western	**1**			**1**		
Central	-0.35	(-0.49- -0.20)	0.001***	-0.40	(-0.53- -0.28)	0.001***
G. Accra	-0.49	(-0.65- -0.33)	0.001***	-0.45	(-0.58- -0.30)	0.001***
Volta	0.16	(-0.009-0.31)	0.038*	0.15	(0.01–0.28)	0.025*
Eastern	0.13	(-0.01-0.28)	0.082	0.11	(-0.02- 0.23)	0.104
Ashanti	-0.31	(-0.45- -0.17)	0.001***	-0.32	(-0.44- -0.20)	0.001***
Brong-Ahafo	0.48	(0.33–0.62)	0.001***	0.44	(0.31–0.56)	0.001***
Northern	0.34	(0.19–0.49)	0.001***	0.28	(0.15- -0.40)	0.001***
Upper East	0.61	(0.44–0.77)	0.001***	0.59	(0.44–0.72)	0.001***
Upper West	0.82	(0.65–0.99)	0.001***	0.77	(0.62–0.91)	0.001***

*1– reference; aCoef.– adjusted coefficient; * Significant level < 0.05; ** Significant level = 0.001; *** Significant level < 0.001*

5. CONCLUSION

Although the evidence shows significant benefits chalked by the 'free' policy in Ghana vis a vis maternal healthcare utilization, the current evidence also shows that the increase in uptake does not translate to the desired outcome of a reduction in stillbirth and neonatal mortality among women who benefit from the policy despite the strong equity gains. Rather, the increase in access to maternal health care appears to have exacerbated the effect of poor quality of care at the delivery points and perhaps at the antenatal care level, thus manifesting in undesirable unborn and newborn outcomes as demonstrated by the evidence. The findings offer an opportunity to increase investment in the policy and by extension the national health insurance scheme to ensure policy continuity to maximize gains towards the achievement of SDG 3 in Ghana and sub-Saharan Africa.

6. STRENGTHS AND LIMITATIONS

Using two rounds of Ghana DHS data afforded the authors a large pool of nationally representative data useful for generalizations. Also, applying multiple models to arrive at a convergence-aided model predictability and sensitivity and added rigor to the current analysis. Nonetheless, propensity score matching assumes that unobserved characteristics are similar and cancel out. Although the GDHS (2008- 2O14) was the most recent data available from the DHS database, the time-lapse as of now suggests that the study findings may be interpreted with caution [6].

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

The authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during writing or editing of the manuscripts.

DATA AVAILABILITY

The datasets generated and/or analysed during the current study are available in the DHS programme repository [https://dhsprogram.com/data/].

ETHICAL APPROVAL AND CONSENT

The study obtained ethical clearance from the DHS Program through online completion of the request form and is publicly available upon request, with no personal identifying information that can be linked to study participants.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. Author JA conceived and designed the study and drafted the manuscript. Authors KA and RBB contributed to the analysis, results interpretation, and the discussion. All authors read and approved the final manuscript as a chapter for the book.

ACKNOWLEDGEMENTS

We are grateful to the Ghana Statistical Service and the Measure DHS programme for all the relevant secondary data used in this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

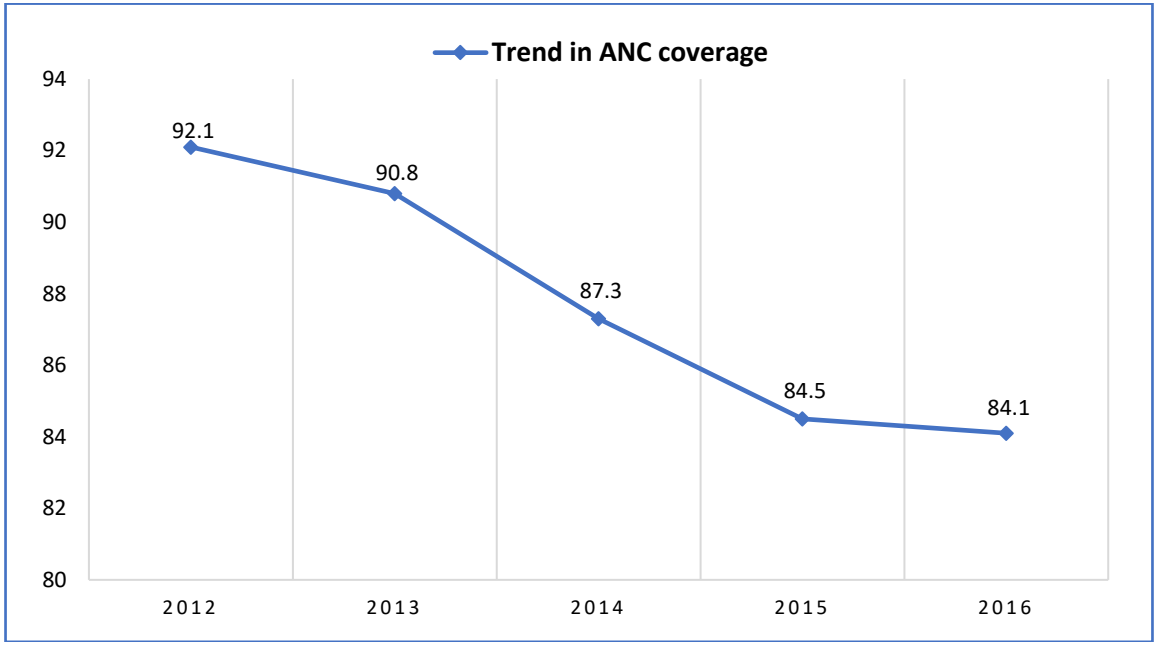
REFERENCES

1. Abdollahpour S, Motaghi Z. Lived traumatic childbirth experiences of newly delivered mothers admitted to the postpartum ward: A phenomenological study. Journal of Caring Sciences. 2019;8(1):23.
2. Alkena L, Chou D, Hogan D, Zhang S, Moller A-B, Gemmill A et al. National, regional, and global levels and trends in maternal mortality between 1990 and 2015 with scenario-based projections to 2030: A systematic analysis by the United Nations Maternal Mortality Estimation Inter-agency Group. Lancet (London, England). 2017;387(10017):462–74.
3. Dickson KS, Darteh EKM, Kyereme-Kumi A. Providers of antenatal care services in Ghana: Evidence from Ghana demographic and health surveys 1988–2014. 2017;17(203):1–9.
4. WHO. World Health Statistic. 2016. Geneva; 2016.
5. UNICEF, UNFPA, UNFPA UNICEF, WBG UN. Trends in maternal mortality 2000 to 2017: Estimates by WHO. World Bank Group and the United Nations Popu- lation Division, Geneva. Geneva. 2019;119.
6. Azaare J, Aninanya GA, Abdulai K, Adane F, Bio RB, Hushie M. Maternal health care utilization following the implementation of the free maternal health care policy in Ghana: Analysis of Ghana demographic and health surveys 2008–2014. BMC Health Services Research. 2024;24(1):207.
7. Olamijulo JA, Olorunfemi G, Okunola H. Trends and causes of maternal death at the Lagos University teaching hospital, Lagos, Nigeria (2007–2019). BMC Pregnancy and Childbirth. 2022;22(1):360.
8. UN. The Millennium Development Goals Report 2013. United Nation. New York; 2013.
9. Banke-Thomas A, Avoka CKO, Gwacham-Anisiobi U, Omololu O, Balogun M, Wright K, et al. Travel of pregnant women in emergency situations to hospital and maternal mortality in Lagos, Nigeria: A retrospective cohort study. BMJ Glob Heal. 2022;7(4):1–16.
10. Gudu W, Addo B. Factors associated with utilization of skilled service delivery among women in rural Northern Ghana: A cross sectional study. 2017;1–10.
11. Cofie LE, Barrington C, Singh K, Sodzi-tettey S, Akaligaung A. Birth location preferences of mothers and fathers in rural Ghana: Implications for pregnancy, labor and Birth Outcomes. 2015;1–8.
12. Kruk ME, Gage AD, Arsenault C, Jordan K, Leslie HH, Roder-DeWan S, et al. High-quality health systems in the Sustainable Development goals era: Time for a revolution. Lancet Glob Heal. 2018;6(11):e1196–252.

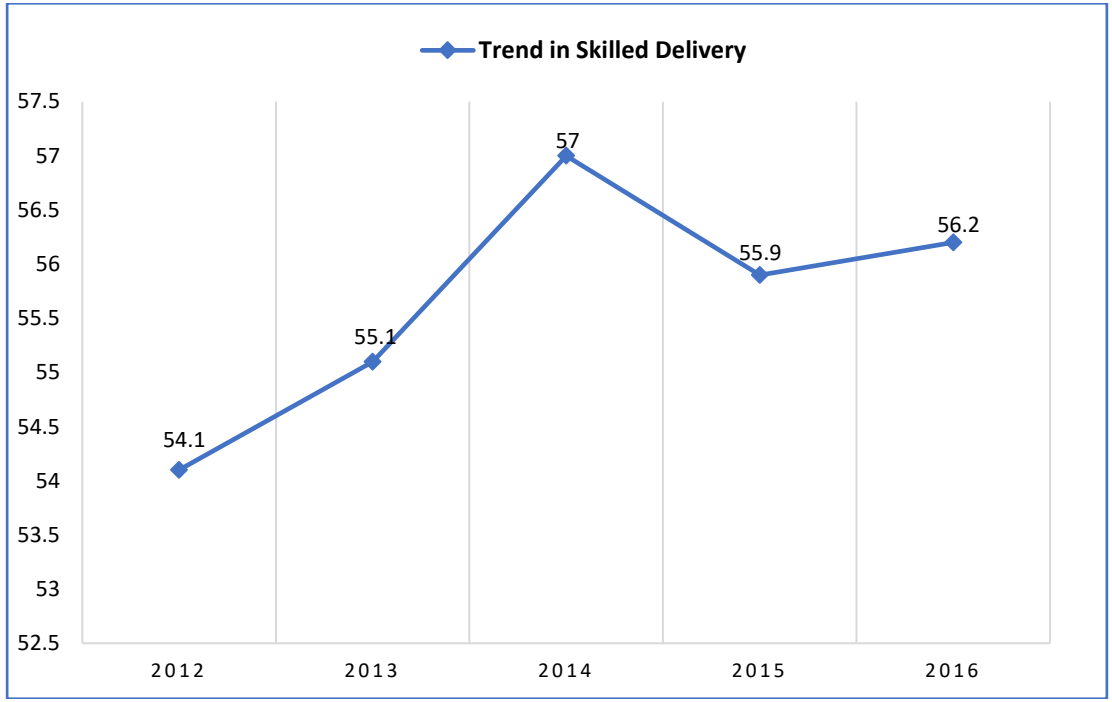
13. Hamal M, Dieleman M, De Brouwere V, de Cock Buning T. Social determinants of maternal health: A scoping review of factors influencing maternal mortality and maternal health service use in India. Public Health Reviews. 2020;41:1-24.
14. Lattof SR, Moran AC, Kidula N, Moller AB, Jayathilaka CA, Diaz T, et al. Imple- mentation of the new WHO antenatal care model for a positive pregnancy experience: A monitoring framework. BMJ Glob Heal. 2020;5(6):1–11.
15. Benova L, Tunçalp Ö, Moran AC, Campbell OMR. Not just a number: examin ing coverage and content of antenatal care in low-income and middle- income countries. BMJ Glob Heal. 2018;3(2):1–11.
16. World Health Organization. A neglected tragedy: The global burden of stillbirths. New York; 2020.
17. Ayanore MA, Pavlova M, Groot W. Focused maternity care in Ghana: results of a cluster analysis. BMC Health Serv Res; 2016. Available:https://doi. org/10.1186/s12913-016-1654-5.
18. Ganle JK. Ethnic disparities in utilisation of maternal health care services in Ghana. Ethn Heal. 2016;21(1):85–101.
19. Fekadu M, Regassa N. Skilled delivery care service utilization in Ethiopia: Analysis of rural-urban differentials based on national demographic and health survey (DHS). Data. 2014;14(4).
20. Turi E, Fekadu G, Taye B, Kejela G, Desalegn M, Mosisa G, et al. The impact of antenatal care on maternal near-miss events in Ethiopia: A systematic review and meta-analysis. Int J Afr Nurs Sci. 2020;13:100246.
21. Haw NJL. Utilization of the Ghana National Health Insurance Scheme and its association with patient perceptions on healthcare quality. Int J Qual Heal Care. 2019;31(6).
22. Ghana Statistical Service (GSS)., Ghana Health Service (GHS) I. Ghana Maternal Health Survey 2017. Accra, Ghana: GSS, GHS, and ICF; 2018.
23. Asante F, Chikwama C, Daniels A, Armar-klemesu M. Evaluating the economic outcomes of the policy of fee exemption for maternal delivery care in Ghana. Ghana Med J. 2010;41(3):110–7.
24. Penfold S, Harrison E, Bell J, Fitzmaurice A. Evaluation of the delivery fee exemption policy in Ghana: Population estimates of changes in delivery service utilization in two regions. Ghana Med J. 2007;41(3):100–9. Available:http://www.ncbi.nlm.nih.gov/pubmed/18470327%0Ahttp:// www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2279083
25. Johnson FA, Frempong-Ainguah F, Padmadas SS. Two decades of maternity care fee exemption policies in Ghana: Have they benefited the poor? Health Policy Plan. 2016;31(1).
26. Witter S, Garshong B. Something old or something new? Social health insur- ance in Ghana. BMC Int Health Hum Rights. 2009;9(1):20. Available:http://bmcinthealthhumrights.biomedcentral.com/articles/https://doi. org/10.1186/1472-698X-9-20
27. Ansong-tornui J, Armar-klemesu M, Arhinful D, Penfold S, Hussein J. Hospital based maternity care in Ghana - findings of a confidential enquiry into maternal deaths. Ghana Med J. 2010;41(3):125–32.

28. Azaare J, Akweongo P, Aryeteey GC, Dwomoh D. Evaluating the impact of maternal health care policy on stillbirth and perinatal mortality in Ghana; A mixed method approach using two rounds of Ghana demographic and health survey data sets and qualitative design technique. Plos One. 2022;17(9):1–23.
Available:https://doi.org/10.1371/journal.pone.0274573
29. Amoro VA, Abiiro GA, Alatinga KA. Bypassing primary healthcare facilities for maternal healthcare in North West Ghana: Socio-economic correlates and financial implications. BMC Health Serv Res. 2021;21(1):1–14.
30. Mugo NS, Mya KS, Raynes-Greenow C. Country compliance with WHO-recommended antenatal care guidelines: equity analysis of the 2015–2016 demography and Health Survey in Myanmar. BMJ Glob Heal. 2020;5(12):1–14.
31. Azaare J, Kolekang AS, Agyeman YN. Maternal health care policy intervention and its impact on perinatal mortality outcomes in Ghana: Evidence from a quasi-experimental design. Public Health. 2023;222:37–44.
Available:https:// doi.org/10.1016/j.puhe.2023.06.035
32. Mosley WH, Chen LC. An Analytical Framework for the Study of Child Survival in developing countries. Popul Develoment Rev. 1984;10:25–45.
33. Hodgins S, D'Agostino A. The quality–coverage gap in antenatal care: Toward better measurement of effective coverage. Glob Heal Sci Pract. 2014;2(2):173–81.
34. University of Ghana. State of the Nation's Health Report. Accra; 2018.
35. Akazili J, Welaga P, Bawah A, Achana FS, Oduro A, Awoonor-Williams JK et al. Is Ghana's pro-poor health insurance scheme really for the poor? Evidence from Northern Ghana. BMC Health Serv Res. 2014;14.
36. Dalinjong PA, Wang AY, Homer CSE. The operations of the free maternal care policy and out of pocket payments during childbirth in rural Northern Ghana; 2017.
37. Abuosi AA, Domfeh KA, Abor JY, Nketiah Amponsah E. Health insurance and quality of care: Comparing perceptions of quality between insured and uninsured patients in Ghana's hospitals. Int J Equity Health. 2016;15(1):76.

SUPPLEMENTARY INFORMATION



Supplementary Fig. 1. Antenatal care attendance, source: GHS report, 2016



Supplementary Fig. 2. Skilled delivery utilization, source: GHS Report, 2016

Biography of author(s)

John Azaare, M.Phil., Ph.D.
Department of Health Service, Policy Planning, Management and Economics, School of Public Health, University for Development Studies, Tamale, Ghana.

He is an academic and health systems consultant with special expertise in health policy impact evaluation. He has over 15 years of experience in healthcare organizational management including emergency and primary healthcare coordination, clinical care, teaching and facilitation. He has authored and co-authored peer-reviewed articles published in international journals of repute and served as a health policy advisor to the World Health Organization (WHO), Zimbabwe Country Office, Harare, Zimbabwe. He has also reviewed several articles for publications in international journals and supervised and examined graduate student's thesis work successfully in policy implementation, maternal and child, healthcare cost and economic burden of diseases. He has travelled widely across Africa and supported countries on health labour market analysis for WHO AFRO including Eswatini, Ghana, Mozambique, Uganda and Zambia. His research interests are health systems strategy and governance, policy impact evaluation, and maternal and child health. He played a lead role recently in supporting the Zimbabwe Ministry of Health and Child Care to roll out the adoption of the E-MOTIVE bundle treatment approach project against postpartum haemorrhage towards tackling maternal mortality in Zimbabwe. He is currently a faculty member of the Department of Health Services, Policy Planning, Management and Economics of the School of Public Health, University for Development Studies, Tamale, Ghana.

Kasim Abdulai, PHD, RD
Department of Clinical Nutrition and Dietetics, Translational Nutrition Research Group, University of Cape Coast, Cape Coast, Ghana.

He is an academic and practitioner of public health nutrition, research, and community engagement. He holds a PhD in Public Health from the University of Ghana. He leverages his expertise to contribute to nutrition and dietetics education at the University of Cape Coast, where he has been an instrumental faculty member since 2018. He has over five years of experience in academia, teaching courses in nutrition and dietetics. He participates in community outreach and health promotion activities, contributing to addressing nutritional challenges in Ghana. His research focuses on maternal nutrition and noncommunicable diseases, with a number of publications to his credit. His commitment extends to serving as the Central-Western Zonal Secretary for the Ghana Academy of Nutrition and Dietetics (GAND). He is also the Executive Director (Operations) for the Coalition of Actors for Public Health Advocacy (CAPHA). Currently, he serves as the Chairman of the Local Organizing Committee-UCC for the upcoming African Nutrition Conference 2024 (ANEC IX) in Ghana.

Dr. Robert Bagngmen Bio
College of Health and Well-Being, Kintampo, Ghana.

He is a Principal Health Tutor with the College of Health and Well-Being, Kintampo, Ghana. He received his PhD and MSc in Public Health from the University of Ghana and the University of the West of England, Bristol, UK. He has extensive working experience in the healthcare industry as a public health officer, with Ghana Health Service. His research interest is in the area of public health in general with a special focus on the epidemiology of infectious diseases of poverty, socio-economic determinants of health, health policy and economics as well as population and reproductive health. He authored and co-authored various peer-reviewed publications in health economics and policy on tuberculosis and maternal health care.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
BMC Health Services Research, 24(207): 2-12, 2024.
Available:https://doi.org/10.1186/s12913-024-10661-5

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1262

Chapter 14
Print ISBN: 978-81-976653-0-1, eBook ISBN: 978-81-976653-1-8

Effective Behavioral Strategies for Managing ADHD in Children: A Comprehensive Review

Veena Shivanna [a*] and Yogeesh Mallenahalli Chikkanna [b]

DOI: https://doi.org/10.9734/bpi/dhrni/v1/1371

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1371

ABSTRACT

Attention deficit hyperactive disorder is the most common psychiatric disorder seen in children in which the child expresses inattentiveness and hyperactivity as the core behaviour characteristics. It affects about 4-12% of all school-age children and is also among the most prevalent chronic psychological condition affecting school-aged children. Managing a child diagnosed with ADHD is quite challenging regardless of the situation presented. Behavioural techniques for managing a child with ADHD are not intuitive for most parents and teachers. It is futile and damaging to try to force a child with ADHD to be like most children. It is possible, however, to limit destructive behaviour and to instil in the child a sense of self-worth that will help overcome negativity. This review article encompasses various techniques for managing a child with ADHD under different practical scenarios and guides parents, teachers and also clinicians to accommodate and modify the behaviour of the child, which includes nondrug therapies, dietary changes, cognitive behavioral therapy, the importance of zinc and other behavioural approaches to manage and modify the child with ADHD.

Keywords: Hyperactivity; impulsivity; cognitive behavioral therapy.

1. INTRODUCTION

Attention deficit hyperactive disorder is the most common neurobehavioral disorder of childhood which affects about 4-12% of all school-age children and is also among the most prevalent chronic psychological condition affecting school-aged children [1,2]. Hyperactivity, inattentiveness and impulsivity are the core

[a] *Department of Paediatric and Preventive Dentistry, Sri Siddhartha Dental College and Hospital, Agalakote, Tumkur, Karnataka, India.*
[b] *Taluk Health Officer, Belur, Karnataka, India.*
**Corresponding author: E-mail: veenayogeesh4@gmail.com;*

behavioral characteristics of this disorder and are evident by the age of 7 years and should have a minimum duration of 6 months to be diagnosed as a disease. These symptoms have been associated with impaired academic performance, low self-esteem, negative occupational outcomes, lower adaptive functioning, social skills problems, aggressive and risky behaviors, and accidental injuries [3,4]. It is estimated that around 60%–100% of children with ADHD also exhibit one or more comorbid disorders that often continue into adulthood [5]. Based on the symptom presentation attention deficit hyperactive disorder is classified into three subtypes:

1.1 Predominantly Hyperactive-impulsive Type

Behaviour marked by hyperactivity and impulsivity, but not inattentiveness. Behaviour is characterized by the following symptoms; • Often fails to pay close attention to details or makes careless mistakes in schoolwork • Often does not seem to listen when spoken directly • Often has difficulty in organising tasks that require sustained mental effort • Often loses things necessary for tasks and activities • Often is easily distracted by external stimuli • Often is forgetful in daily activities [6].

1.2 Predominantly Inattentive Type

Behaviour marked by inattentiveness, but not hyperactivity and impulsivity behaviour is characterised by the following symptoms.

Often fidgets with hands or feet, or squirms in seat.

Often runs about or climbs excessively inappropriate situations.

Often has difficulty playing or engaging in leisure activities quietly.

Often talks excessively, and blurts out answers even before the questions are asked.

Often interrupts in calm class. Has difficulty awaiting his turn.

Often intrudes on others [6].

1.3 Combination Type

A combination of hyperactivity/impulsivity and inattentive symptoms. This is the most common type of ADHD. In order to make a valid diagnosis these symptoms must be present for at least 6 months before the age of 7 years to a degree that is inconsistent with the developmental level of a child and causes impairments in at least 2 different settings. Thus there must be clear evidence of clinically significant impairment in social, academic or occupational functioning. Peer rejection and disruptive behaviours which can lead to academic and social difficulties are the most valid problems of the disorder. Other long-term

consequences include higher rates of accidents as well as alcohol and drug abuse, and criminal behaviours when Attention Deficit Hyperactive Disorder is accompanied by conduct problems [2,7,6]. Behavioural techniques for managing a child with ADHD are not intuitive for most parents and teachers. To learn them, caregivers may need help from qualified mental health care professionals or from ADHD support groups. At first, the idea of changing the behaviour of a highly energetic, obstinate child is daunting. It is possible, however, to limit destructive behaviour and to instil in the child a sense of self-worth that will help overcome negativity.

2. REASONS FOR CONSIDERATION OF NON-PHARMACOLOGICAL TREATMENT

- Multimodal treatment approaches are recommended by several national and international clinical guidelines.
- Problems of public scepticism/cynicism about ADHD management. Public opinions have become divided, and several controversies have emerged around the wide variations in medical and non-orthodox practices that have been promoted and implemented in the management of ADHD. Some people have gone as far as querying the existence of ADHD as a bona fide medical diagnosis.
- ADHD medications do not result in universally effective responses. It has been reported that 10–30% of CYP (children and young people) would not respond to ADHD stimulant medications. Another 10% of ADHD children would be unable to tolerate the medications due to significant side effects.

Non-stimulant medications provide alternative options for pharmacological therapy, but they are generally less effective and not as widely studied compared to stimulants. The efficacy of stimulant medications is lower in younger children and is associated with a higher burden of side effects. Additionally, although core symptoms may respond, other important variables like academic achievement and social relationships can remain unchanged.

- Parental and some Clinicians' perceptions. Some parents and clinicians are reluctant to recommend ADHD medication use due to concerns about undesirable long-term side effects and express preference for nonmedication options.
- Some authors have reported that 58% of carers refuse ADHD medications for their CYP with ADHD.
- Problematic low therapeutic compliance during adolescence.
- Pharmacotherapy is less effective for managing the most common co-morbidities of oppositional and conduct problems or challenging behavior.
- Pharmacologic treatment is less effective among preschool children.
- Adverse effects of pharmacological treatments Mild to moderate adverse effects are common with all pharmacological agents used in the treatment of ADHD, including disturbances of sleep, growth, appetite, blood pressure and heart rate. More severe side effects such as psychotic symptoms are also rarely reported. A few observational studies have also

reported increased risks of seizures, tics, depression and suicidal attempts associated with pharmacologic treatment of ADHD.

- Higher level of acceptability. Some studies have confirmed high levels of acceptability. Behaviour therapy alone when compared to pharmacology treatment, and there are higher risks of patients discontinuing ADHD medication use compared to placebo [8-10].

Table 1. Summary of Evidence for other ADHD-related behavioral problems

	Single modalities combinations			
01	Behavioural therapy (BT)	Moderate ES for typically unblinded parent ratings	Effect size near 0 and non-significant for probably blinded measurements	BT and stimulants: superior to stimulants or non-stimulants
02	Computer-based Cognitive training (CT)	CT game for attention: reduction in the clinician ADHD-RS and functional EEG changes. All types of CT: Significant effects on total ADHD ([SMD] = 0.37) and inattentive symptoms (SMD = 0.47) for unblinded raters.	CT for working memory: either no effect or mixed effects on ADHD symptoms. All types of CT: Small ES for total ADHD symptoms ([SMD] = 0.2) and inattentive symptoms (SMD = 0.32) for blinded raters. All types of CT: No significant effects on H/I symptoms.	Stimulants and combined treatment groups with CT: More effective in improving ADHD symptoms
03	Cognitive Behaviour Therapy (CBT)		Group-based CBT: Mixed effects on ADHD symptoms and functional impairment	CBT and stimulants: improve core ADHD symptoms
04	NeuroFeedback [NF]	Medium to large ES on inattention [SMD = 0.64 to 0.80), while ES for H/I was medium [SMD = 0.50–0.61)	The effect is mixed for core ADHD symptoms, academic & social skills	

Single modalities combinations		
05	Psychoeducation	Parents group Psychoeducation: Significant reduction of ADHD symptoms (p = 0.001)
06	Meditation	Low to moderate efficacy (Hedge's g = −0.44, 95% CI −0.69 to compared −0.19, I20%) to control conditions.

**Note: BT – Behavioural therapy; CT – Computer-based Training; ES – Effect size (measured by SMD); H/I – Hyperactivity/Impulsivity symptoms; SMD – Standardized Mean Difference.*

2.1 Behavioural Techniques at Home

Bringing up a child with ADHD, like bringing up any child, is a process. No single point is ever reached where the parent can sit back and say, "That's it. My child is now OK, and I don't have to do anything more." The child's self-esteem will evolve with an increasing ability to step back and consider the consequences of an action and then control that action before taking it. But this does not happen overnight. A growing child with ADHD is different from other children in very specific ways, presenting challenges at every age [11-13,6].

2.2 Setting Priorities for the Parent

Parents must first establish their own levels of tolerance. Some parents are easygoing and can accept a wide range of behaviors, while others cannot. To help a child achieve self-discipline requires empathy, patience, affection, energy, and toughness. Some tips to help parents include:

- Parents should prepare a list giving priority to those behaviors they think are the most negative, such as fighting with other children or refusing to get up in the morning. The least negative behaviors on the bottom of the list should be ignored temporarily or even permanently (refusing to wear anything but red T-shirts).
- Certain odd behaviors that are not hurtful to the child or to others may be an indication of creative or humorous attempts to adapt (making up silly songs or drawing violent pictures). These should be accepted as part of the child's unique and positive development, even if they seem peculiar to the parent [6].
- It is important to keep in mind that no one is a saint. Loving parents who occasionally lose their tempers will not damage their children forever. In fact, non-abusive open disapproval or dismay is far less destructive to both parent and child than harboring resentment beneath a false calm.

3. ESTABLISHING CONSISTENT RULES FOR THE CHILD

Parents must be as consistent as possible in their approach to the child, which should reward good behavior and discourage destructive behavior. Rules should be well-defined but flexible enough to incorporate harmless idiosyncrasies. It is very important to understand that children with ADHD have much more difficulty adapting to change than children without the condition. (For example, the child should do homework every day but might choose to start it after a TV show or computer game) [6]. Parents should establish a predictable routine, and provide a neat, stable home environment (particularly in the child's room).

3.1 Managing Aggression

Some useful tips for managing aggression include:

- Parents should try to give little attention to mildly disruptive behaviors that allow this energetic child to let off some harmless steam. The parent will also be wasting energy that will be needed when the negative behavior becomes destructive, abusive, or intentional.
- The use of "time-out", isolating the child immediately for a short period of time, is an effective measure for allowing both the caregiver and the child to cool down. The child should immediately (and without emotion) be removed from a situation in which they are endangered or endangering others. The child should view time out as a way of cooling off and getting a distance from their behavior, not as isolation from others [6].
- To channel physical aggression and impulsivity in a toddler with ADHD, the parents must teach them to use verbal responses (A parent may need to allow verbal responses that would be unacceptable in another child).
- When the child becomes older and if the verbal responses become intentionally abusive and socially undesirable, the parent must redirect this form of aggression into more acceptable activities, such as competitive one-on-one sports, energetic music, video games, or big colorful paintings. Competitive video games, such as sports games, may also be an option.
- Sometimes a parent can anticipate situations when a child with ADHD is likely to misbehave, but all too often the child explodes for no apparent reason. If the blowup occurs in public, the parents should complete their activities and leave as quickly as possible [6].

3.2 Establishing a Reward System

Children with ADHD respond particularly well to reward systems. One study reported that they performed equally well when encouraged either by a direct reward for a correct response or with the use of a system called response-cost. With this system, the child is given the reward first and allowed to keep it if their behavior remains appropriate Some suggested tips for rewarding the ADHD child are [14,15]:

- Create charts with points or stars for good behavior or for completed tasks. It is important to give points for even simple positive behaviors, which may be taken for granted by other children (responding happily to a change in plans, changing an obscenity to a more acceptable expletive).
- Rewards for any child can include playing a favourite game, extending bedtime by an hour, or allowing an extra half-hour of TV [6].
- Rewards of food or gifts should be used infrequently, if at all. They can create other problems, such as being overweight, having a bad diet, or making continuous demands for objects.
- A reward system should rotate different types of rewards because such children are easily bored.
- Children with ADHD respond better to small rewards promised in the short-term than large rewards offered in the future. One approach that uses both short- and long-term rewards is a system that gives the child points for specific positive behaviors. As the children accumulate points, they can use them for larger tangible rewards, such as a favourite video game or CD.
- Rewards should be promised only when caregivers are fairly certain they can follow through. Children with ADHD respond with much greater frustration than children without ADHD to disappointment and are likely to have a strong (and noisy) negative reaction.

A parent must remember that this response is part of the child's make-up and not necessarily in their control. Improving concentration and attention Children with ADHD perform significantly better when their interest is engaged. Parents should be on the lookout for activities that hold the child's concentration. Options include swimming, tennis, and other sports that focus attention and limit peripheral stimuli. (Children with ADHD may have difficulty with team sports that require constant alertness, such as football or basketball.) [6].

Martial arts, such as Tae Kwon Do, can also offer an appropriate and controlled emotional outlet, help to focus attention and teach self-restraint, self-discipline, and tolerance. Learning an instrument can help a child to develop a more rhythmic and balanced sense of self [16].

4. MANAGEMENT AT SCHOOL

Even if a parent is successful in managing the child at home, difficulties often arise at school. The ultimate goal of any educational process should be the happy and healthy social integration of children with ADHD with their peers [16-17].

4.1 Preparing the Teacher

Although teachers can expect at least one student in every classroom to have ADHD, there is generally little training that prepares them for managing these children. The teacher should be prepared for certain behaviours in the child with ADHD [6]:

- Students with ADHD are often demanding, talkative, and highly visible.
- Inattention is a major factor in low academic performance and can cause children to frequently forget homework or miss assignments. Children with ADHD often require frequent reminders or visual cues (such as posters) for rules and regulations. Having the child sit in the front of the classroom may be helpful for both increasing attention and reducing noisy activity.
- Lack of fine motor control makes taking notes very difficult, and handwriting is often poor. Using a computer can compensate for this.
- Rote memorization and math computation, which require following a set of ordered steps, are often difficult. (Children with ADHD may do better with math concepts) [6].
- Many children with ADHD respond well to school tasks that are rapid, intense, novel, or of short duration (such as spelling bees or competitive educational games), but they almost always have problems with long-term projects where there is no direct supervision.

4.2 The Role of the Parent in the School Setting

The parent can help the child by talking to the teacher before the school year starts about their child's situation. The first priority for the parent is to develop a positive, not adversarial, relationship with the child's teacher. Finding a tutor to help after school may also be helpful.

5. SPECIAL EDUCATION PROGRAMS

The Individuals with Disabilities Education Act (IDEA) requires the school to identify and evaluate children who may need help and to provide special services. However, parents sometimes report pressure from the school to put their children on medication or force them into special classrooms without clear educational justification. The schools in these cases, may be acting illegally. High-quality special education can be extremely helpful in improving learning and developing a child's sense of self-worth. However, programs vary widely in their ability to provide quality education.

Parents must be aware of certain limitations and problems with special education:

- Special education programs within the normal school setting often increase the child's feelings of social alienation [6].
- If the educational strategy focuses only on abnormal behavior, it will fail to take advantage of the creative, competitive, and dynamic energy that often accompanies ADHD behavior.
- There is no federally funded special education category specifically targeted to ADHD.

The best approach may be to treat the syndrome as a variant of the norm and train teachers to manage these children within the context of a normal classroom. Special programs are also required under the Rehabilitation Act and by the

Americans with Disabilities Act (ADA) for students at institutions of higher learning. It is the student's responsibility, however, to inform the administration at their college or university that they need such services [17,18].

The drugs under review were primarily amphetamines and methylphenidate (Ritalin, Concerta, and other brands). These agents are closely related members of the class of sympathomimetic amines, the structures of several of which are shown in the Molecular Structures of Sympathomimetic Amines. These compounds exert potent stimulant effects on the cardiovascular and central nervous systems.

6. DIETARY APPROACHES

A number of diets have been suggested for people with ADHD. Several well-conducted studies have failed to support the dietary effects of sugar and food additives on behavior, except possibly in a very small percentage of children. Still, various studies have reported behavioral improvement with diets that restrict possible allergens in the diet. Parents may want to discuss with their doctor implementing an elimination diet of certain foods that would not be harmful and that might help [6].

Additives and foods that parents and studies report as possible triggers of behavioral changes include:

- Any artificial colorings (particularly yellow, red, or green)
- Other chemical additives -- for example, BHT or BHA
- Milk
- Chocolate
- Eggs
- Wheat
- Foods containing salicylates, including all berries, chili powder, apples and cider, cloves, grapes, oranges, peaches, peppers (bell & chili), plums, prunes, tomatoes.

Dietary strategies evaluated in ADHD include elimination of synthetic food additives, and sensitizing food allergens or sugar. Dietary supplementation studies in ADHD include the use of vitamins, minerals, omega-3 and omega-6 fatty acids, amino acids and natural metabolites [19].

Feingold Diet: The most well-known diet for ADHD is the Feingold diet, a salicylate- and additive-free diet, which requires rigorous vigilance over a child's eating habits. This diet also prohibits aspirin, which contains salicylates. Some parents report success with this diet, although it may be difficult to impose [6]. It is certainly wise, in any case, to avoid food with artificial colors and flavors and to provide a healthy balance of fresh, natural foods. Essential fatty acids Omega-3 fatty acids, found in fatty fish and certain vegetable oils, are important for normal brain function and may have some benefits for people with ADHD. It is not clear if

supplements of fatty acid compounds, such as docosahexaenoic acid (DHA) and eicosapentaneoic acid (EPA), provide any advantages.

Zinc: Zinc is important for the metabolism of certain neurotransmitters that play a role in ADHD, and deficiencies may be associated with some cases of ADHD. Long-term use of zinc, however, can cause anemia and other side effects in people without deficiencies and it has no effect on ADHD in these patients. In any case, testing for trace minerals, such as zinc, is not standard procedure when evaluating children suspected to have ADHD [6].

Sugar: Although parents often blame sugar for causing children to become impulsive or hyperactive, a number of studies strongly indicate that sugar plays no role in hyperactivity.

7. FEEDBACK APPROACHES

Techniques that use biological or auditory feedback may be effective tools for improving children's attention [20]. Other Non-Drug Therapies A number of alternative approaches are tried by children and adults with mild ADHD symptoms. For example, daily massage therapy may help some people with ADHD feel happier, fidget less, be less hyperactive, and focus on tasks. Other alternative approaches that may be helpful include relaxation training, meditation, and music therapy. Based on existing evidence, these treatments may be helpful for symptom management but are not proven to benefit the underlying disorder [21-24].

7.1 Herbs and Supplements

A number of parents resort to alternative remedies as an alternative to psychostimulants and other drugs. These products include St. Johns wort, ginkgo biloba, panax ginseng, melatonin, and pine bark extract. Based on; existing evidence, however, none can be recommended, particularly for children. Generally, manufacturers of herbal remedies and dietary supplements do not need FDA approval to sell their products. Just like a drug, herbs and supplements can affect the body's chemistry, and therefore have the potential to produce side effects that may be harmful [6]. There have been a number of reported cases of serious and even lethal side effects from herbal products. Always check with your doctor before using any herbal remedies or dietary supplements [25,26].

7.2 Neurofeed Back

An alternative treatment for ADHD Neurofeedback EEG biofeedback was developed as an additional or alternative treatment option for children, proceeding from a perspective that ADHD is a neurologically based disorder limiting the capacity for attention and behavioural control. Neurofeedback treatments within child and adolescent psychiatry began about 30 years ago. Two training protocols-theta/beta training and training of Slow Cortical Potentials (SCPs)-are typically used in children with ADHD. In the resting EEG (relaxed

awake state, usually with eyes closed), increased slow wave activity (theta, 4-8 Hz) and/or reduced alpha (8-13 Hz) and beta (13- 30 Hz) activity, especially in central and frontal regions, might be associated with ADHD [6]. This indicates cortical underarousal, particularly in mixed subtypes. Thus, it seems plausible that in a paradigm often applied in ADHD, the goal is to decrease activity in the theta band and to increase activity in the beta band (or to decrease theta/beta ratio) at the vertex (electrode Cz), i.e., activating and maintaining a state of cortical arousal (''tonic activation'') [27,28].

8. CONCLUSION

This review article concludes that behaviour management techniques for children with ADHD are quite different from other healthy children. Apart from behaviour modifications certain nondrug therapies like zinc supplements, and dietary modifications also play a vital role in modifying the behaviour of children with ADHD [6].

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Baumgaertel A, Wolraich ML, Dietrich M. Comparison of diagnostic criteria for attention deficit disorders in a German Elementary School Sample. J Am Acad Child adolesc Psychiatry. 1995;34(5):659-638.
2. Cantwell DP. Attention deficit disorder: A review of the past 10 years. J Am Acad Child Adolesc Psychiatry. 1996;35(8):978-987.
3. Faraone SV, Radonjić NV. Neurobiology of attention deficit hyperactivity disorder. Tasman's Psychiatry. 2023 Jul 29:1-28.
4. Gnanavel S, Sharma P, Kaushal P, Hussain S. Attention deficit hyperactivity disorder and comorbidity: A review of literature. World Journal of Clinical Cases. 2019 Sep 9;7(17):2420.
5. Gnanavel S, Sharma P, Kaushal P, Hussain S. Attention deficit hyperactivity disorder and comorbidity: A review of literature. World Journal of Clinical Cases. 2019 Sep 9;7(17):2420.
6. Shivanna V, Chikkanna YM. Behavioral management in child with Attention Deficit Hyperactive Disorder-Review. of. 2016;5:2.
7. Goldman LS, Genel M, Bezman RJ, Slanetz PJ. Diagnosis and treatment of attention-deficit/hyperactive disorder in children and adolescents. JAMA. 1998;279(14):1100-1105.

8. Ogundele, Ayyash FH. ADHD in children and adolescents: Review of current practice of non-pharmacological and behavioural management. AIMS Public Health 2023 :10(1) 35–51.
9. Bierderman J. Attention deficit /hyperactive disorder: A Life-Span Perspective. J Clin Psychiatry. 1998;59(7):4-16.
10. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics. 2009;124(2):717-728.
11. Biederman J, Melmed RD, Patel A, et al. A randomized, double-blind, placebocontrolled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. Pediatrics. 2008;121(1):e73-84.
12. Bostic JQ, Prince JB. Child and adolescent psychiatric disorders. In: Stern TA, Rosenbaum JF, Fava M, Biederman J, Rauch SL, eds. Massachusetts general hospital comprehensive clinical psychiatry. 1st ed. Philadelphia, Pa: Mosby Elsevier; 2008:chapter 69.
13. Gould MS, Walsh BT, Munfakh JL, et al. Sudden death and use of stimulant medications in youths. Am J Psychiatry. 2009;166(9):992-1001.
14. Hamilton SS, Armando J. Oppositional defiant disorder. Am Fam Physician. 2008;78(7):861-866.
15. Heinrich H, Gevensleben H, Strehl U. Annotation: Neurofeedback - train your brain to train behaviour. J Child Psychol Psychiatry. 2007;48(1):3-16.
16. Jensen PS, Arnold LE, Swanson JM, et al. 3-year follow-up of the NIMH MTA study. J Am Acad Child Adolesc Psychiatry. 2007;46(8):989-1002.
17. Millichap JG. Etiologic classification of attention-deficit/hyperactivity disorder. Pediatrics. 2008;121(2):e358-365.
18. Nissen SE. ADHD drugs and cardiovascular risk. N Engl J Med. 2006;354(14):1445-1448.
19. Mosholder AD, Gelperin K, Hammad TA, Phelan K, Johann-Liang R. Hallucinations and other psychotic symptoms associated with the use of attention-deficit/hyperactivity disorder drugs in children. Pediatrics. 2009;123(2):611-616.
20. Sharma A Gerbarg P L Brown P R. Non-pharmacological treatments for ADHD in Youth. Adolesc Psychiatry (Hilversum). 2015 ; 5(2): 84–95
21. Nigg JT, Breslau N. Prenatal smoking exposure, low birth weight, and disruptive behavior disorders. J Am Acad Child Adolesc Psychiatry. 2007;46(3):362-369.
22. Perrin JM, Friedman RA, Knilans TK, Black box working group, section on cardiology and cardiac surgery. Cardiovascular monitoring and stimulant drugs for attention-deficit/hyperactivity disorder. Pediatrics. 2008;122(2): 451-453.
23. Pliszka S, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/ hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46(7):894-921.
24. Prince JB, Spencer TJ, Wilens TE, Biederman J. Pharmacotherapy of attention-deficit/hyperactivity disorder across the life span. In: Stern TA, Rosenbaum JF, Fava M, Biederman J, Rauch SL, eds. Massachusetts

General Hospital Comprehensive Clinical Psychiatry. 1st ed. Philadelphia, Pa: Mosby Elsevier. 2008;chap 49.

25. Rader R, McCauley L, Callen EC. Current strategies in the diagnosis and treatment of childhood attention-deficit/hyperactivity disorder. Am Fam Physician. 2009;79(8):657-665.
26. Steiner H, Remsing L, Work group on quality issues. Practice parameter for the assessment and treatment of children and adolescents with oppositional defiant disorder. J Am Acad Child Adolesc Psychiatry. 2007;46(1):126-141.
27. Swanson JM, Elliott GR, Greenhill LL, et al. Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. J Am Acad Child Adolesc Psychiatry. 2007;46(8):1015-1027.
28. Bakhshayesh AR, Hansch S, Wyschkon A, Rezai MJ, Esser G. Neurofeedback in ADHD: A single-blind randomized controlled trial. Eur Child Adolesc Psychiatry. 2011;20(9):481-491.

Biography of author(s)

Dr. Veena Shivanna (Associate Professor)
Department of Paediatric and Preventive Dentistry, Sri Siddhartha Dental College and Hospital, Agalakote, Tumkur, Karnataka, India.

Research and Academic Experience: She has 11 years of research and academic experience.

Research Specialization: Her research domain involves pediatric and preventive dentistry.

Number of Published papers: She has published 18 papers in several reputed journals.

Any other remarkable point(s): She has a deep interest in the dental management of special children.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Journal of Dental and Oral Health, 2(3): 037, 2016.
Available: https://scientonline.org/abstract/21286/Behavioral-Management-in-Child-with-Attention-Deficit-Hyperactive-Disorder--Review

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/1371

London Kolkata Tarakeswar

India: Guest House Road, Street no - 1/6, Hooghly, West Bengal, India (Reg. Address),
Diamond Heritage Building, 16, Strand Road, Kolkata, 700001 West Bengal, India (Corporate Address),
Tele: +91 7439016438 | +91 9748770553, Email: director@bookpi.org,
(Headquarters)

UK: 27 Old Gloucester Street London WC1N 3AX, UK,
Fax: +44 20-3031-1429, Email: director@bookpi.org,
(Branch office)