



Strengthening Vaccine Management in a Resource-Limited Setting: A Study of Healthcare Workers' Practices in Wau County, Western Bahr El Ghazal State, South Sudan

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ABSTRACT

Background: Effective Vaccine Management (EVM) is crucial for maintaining vaccine potency and protecting children from preventable diseases. A 2019 assessment using World Health Organization (WHO) criteria identified significant deficiencies in Wau county's vaccine management practices, with a score of only 56% across nine key domains. These domains include vaccine storage temperature, arrival processes, storage capacity, infrastructure, equipment, maintenance, stock management, distribution, and supportive functions.

Objective: This study aims to assess the knowledge levels, practices, and challenges affecting vaccine management among healthcare workers in public health facilities in Wau county, Western Bahr El Ghazal state, South Sudan.

Method: A descriptive cross-sectional research design was employed, collecting data from 27 public health facilities, including primary health care centers, units, hospitals, and cold chain centers. A self-administered questionnaire targeted 52 healthcare workers involved in vaccine management. Descriptive statistics, including mean, standard deviation, frequency, and percentages, were used for data analysis.

Results: The study revealed knowledge and practice gaps related to EVM. While 69% of respondents had some knowledge of Vaccine Vial Monitors (VVMs), this was below the WHO benchmark of 80%. Notably, 44% were unaware of vaccine stock availability, and 48% lacked knowledge of temperature recording. Only 42% adhered to the recommended EVM practices from WHO and the Ministry of Health. Key challenges identified included cold chain equipment (mean: 3.8), lack of training and supervision (mean: 3.78), insufficient management support (mean: 3.63), and logistical issues (mean: 3.58). Policy-related challenges were perceived as less influential (mean: 2.76).

Conclusion: The study highlights significant shortcomings in EVM practices among healthcare workers in Wau county, particularly in areas such as vaccine stock awareness and temperature recording. Adherence to WHO recommendations is below target levels, and critical challenges persist, including inadequate cold chain equipment, limited training, and logistical issues. Addressing these gaps through targeted training, supportive supervision, improved resource allocation, and policy revisions is essential for strengthening EVM practices and ensuring optimal vaccine effectiveness.

Recommendations: To enhance EVM practices in Wau county, a multi-faceted approach is essential. Policymakers should prioritize investments in cold chain equipment and training programs that align with WHO best practices.

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Strengthening management support through clear policies and effective communication is crucial. Additionally, reviewing existing policies is necessary to address operational gaps and optimize logistics through stakeholder collaboration. Implementing these recommendations will empower healthcare workers with the resources and knowledge needed to manage vaccines effectively, thereby protecting children from preventable diseases.

Keywords: EVM; Vaccine; County; Public health facilities; Vaccine coverage; Western Bahr El ghazal state; South Sudan

Abbreviations: BCG: Bacillus Calmette-Guérin; CCE: Cold Chain Equipment; CHD: County Health Department; DPT3: Diphtheria Pertussis Tetanus; EVM: Effective Vaccine Management; GAVI: Global Alliance Vaccine Immunization; HFs: Health Facilities; MDVP: Multi-Dose Vial Policy; PHCCs: Primary Health Care Centre; PHCUs: Primary Health Care Units; OPV3: Oral Polio Vaccine Third Dose; SOPs: Standard Operating Procedures; SSPS: Statistical Package for Social Sciences; UNICEF: United Nations Children's Education Fund; VPD: Vaccine Preventable Diseases; VVM: Vaccine Vial Monitor; WBeGs: Western Bhar El Ghazal state; WHO: World Health Organization

INTRODUCTION

Vaccines have significant importance in the prevention and control of many communicable diseases and therefore underpin global health security. Globally, vaccines have been used to prevent and control various diseases, including Vaccine-Preventable Diseases (VPD) for children. In sub-Saharan Africa, the BCG vaccination coverage against diseases at childbirth had varying percentages at 92%, 91%, 89%, 83%, and 52% in Kenya, Uganda, Rwanda, Burundi, and South Sudan, respectively, while Oral Polio Vaccine (OPV3) vaccination coverage was at 93%, 91%, 89%, 88%, and 50% for Burundi, Rwanda, Kenya, Uganda, and South Sudan, respectively [1].

However, effective application of vaccines considerably relies on their proper management. Vaccine management is referred to as a process in which vaccines are procured, shipped, and transported until they reach the lowest health facility point, where utilization and administration to the client is performed. Good vaccine handling and storage are vital factors in preventing and eradicating VPD. Incorrect handling and storage of vaccines can create a need for re-vaccination of several clients, incurring huge financial losses. Likewise, poor storage and handling of vaccines lead to reduced vaccine potency, resulting in inadequate immune responses in clients and eventually leading to less protection against VPD. Thus, good inventory management and handling of vaccines by health workers play a significant role in improving the health of the community.

Both WHO and UNICEF launched an initiative for Effective Vaccine Management (EVM) in 2010 to help countries improve vaccine management, aiming for 80% as a target to be met to deem the country performing well in this area. According to WHO/UNICEF annualized routine immunization data from January to May 2021 in South Sudan, the coverage of DPT3 was reported to be 78%. Despite improvements in immunization coverage over the years in South Sudan, the country still ranks lowest in the East African region [2].

Therefore, WHO, UNICEF, and the Global Alliance for Vaccines and Immunization (GAVI) are making intensive efforts to prioritize vaccine supply improvement and the country's

performance through EVM. In addition, the Ministry of Health of South Sudan's 2016-2025 framework strategy comprises four main targets, including consistent vaccine supply chain improvement, quality management, optimization, and innovation.

In South Sudan, immunization coverage has improved in most parts of the state's health facilities. However, counties in the Western Bahr El-Ghazal state (WBeGs), including Wau county, have reported measles outbreaks in the past five years consecutively. While this could be due to many factors, identified gaps in EVM may have been a contributing factor. In the 2019 assessment as per WHO criteria, five indicators in Wau county showed performance lower than 80% for areas such as stock management, maintenance, vaccine distribution, vaccine management, information management, and support functions. Likewise, human resource capacity has been reported to be poor, especially at lower levels, with limited capacity to utilize the available guidelines [3].

As an interventional strategy, the government and partners have trained vaccine handlers, improved vaccine storage infrastructure, and enhanced equipment maintenance. However, since the last assessment in 2019, no study has been done to determine the current situation in the five WHO domains of EVM. Therefore, this study was conducted to identify

- The knowledge level of health personnel on EVM in health facilities.
- Vaccine handlers' practices implemented in relation to WHO standard criteria for effective vaccine management.
- Major challenges affecting vaccine management in Wau county's health facilities.

It is envisaged that this study will provide information that may be utilized by State Ministry of Health authorities, health partners, and scholars for decision-making mechanisms and improvement of effective vaccine management. These efforts will contribute to the improvement in the quality of the Expanded Programme on Immunization (EPI), especially in areas of cold

chain infrastructure and equipment, vaccine storage, human resources, and overall supply chain management [4].

MATERIALS AND METHODS

Study setting

Data was collected from all twenty-seven (27) health facilities that provided immunization services in Wau county, Western Bahr El Ghazal State, South Sudan. Both lower-level health facilities (primary health care centers and primary health care units) and higher-level health facilities (hospitals, county cold chain, and state cold chain) providing immunization services participated in the study.

Wau county, Western Bahr El Ghazal State, South Sudan, is home to 246,273 people, with a population density of 19.251 people/km² according to estimated population projections for 2021 [5].

Study design and participants

A descriptive cross-sectional using quantitative methods was conducted for all the twenty-seven (27) health facilities with functional cold chain in Wau county Western Bahr El Ghazal State, South Sudan. From the twenty-seven (27) health facilities, participants considered per facility were vaccinator, nurse or cold chain technician [6].

Sampling

In all the twenty-seven (27) health facilities, two health workers responsible for vaccine handling and management were considered making a total of fifty-two (52) participants.

Data collection tool and data collection procedure

The study questionnaire comprised four parts: A demographic section with nine items, knowledge with eleven items, practice with twenty-four items, and major challenges with twenty items. The questionnaires were developed from the WHO/IVB/05.02

version. The respondents were identified with the help of four assessors selected from the County Health Department (CHD) and trained by the researcher to facilitate the administration of the questionnaires in the health facilities.

The hard copy questionnaires, after being reviewed by the supervisors, were printed and delivered by the assessors physically to each respondent in their respective health facilities. At each health facility, the vaccine handlers explained the purpose of the questionnaire and assured respondents of the confidentiality of their information. Each respondent was given a consent form to sign before filling out the questionnaire, which took approximately 15 to 20 minutes to complete [7].

Methods of data analysis

The collected data using questionnaire scripts were cleaned, coded, edited and using SPSS software, Version Twenty-six. Accordingly, simple descriptive statistics namely percentage, frequency, mean and standard deviation is computed to analyses the data.

RESULTS AND DISCUSSION

Demographic profile of health workers

From the five (5) types of health facility surveyed, 38 (73%) were lower-level health facilities (PHCCs and PHCUs) and 14 (27%) were higher level health facilities (hospitals, county cold chain and state cold chain) providing immunization services. Most respondents 36 (69%) were aged between 31 to 50 years. Furthermore, 34 (66%) of the health personnel were males, most of the health workers 22 (43%) had attained secondary education, and 21 (40%) reached tertiary/university level. Importantly, 32 (62%) had more than five years work experience (Tables 1 and 2).

Table 1: Demographic profile of the respondent: Level of health facilities and job title.

Health facilities and job title (n=52)	Frequency	Percentage
Health facilities		
PHCU	20	38
PHCC	18	35
Hospital	9	17
County cold chain	3	6
State cold chain	2	4
Job title of the respondent		
Vaccinators	19	38

Nurses	13	25
Clinical officer	15	28
Cold chain assistant	5	9

Table 2: Demographic profile of the health workers.

Background characteristics	Frequency (n=52)	Frequency	Percentage
Age group (Years)			
21-30	1	3	
31-40	14	26	
41-50	22	41	
51-60	3	6	
>61	12	25	
Gender			
Male	34	66	
Female	18	34	
Education level			
Primary	9	17	
Secondary	22	43	
Tertiary institution	18	34	
Bachelor's degree	3	6	
Marital status			
Single	11	22	
Married	34	65	
Widowed	4	7	
Divorced	3	6	
Experience			
0-2	19	36	
2-5	1	2	
>5	32	62	

Knowledge of health workers in handling vaccines in health facilities

The survey of 52 participants regarding their knowledge of Effective Vaccine Management (EVM) revealed a mixed understanding across several key areas.

A majority (69%) reported knowledge of Vaccine Vial Monitors (VVM), while 46% acknowledged the importance of vaccine availability in health facilities. Knowledge of how to forecast vaccine requirements was notably high at 85%. Awareness of the Multi-Dose Vial Policy (MDVP) was present in 73% of participants. However, only 52% were knowledgeable about proper temperature monitoring practices, and 77% understood the significance and function of Cold Chain Equipment (CCE) [8].

These findings highlight both strengths and weaknesses in the participants' knowledge of EVM. The high levels of understanding regarding vaccine forecasting and VVM usage suggest a solid foundation in critical areas that directly impact vaccine effectiveness. Conversely, the lower awareness about vaccine availability and temperature monitoring indicates significant gaps that could compromise immunization efforts. This suggests an urgent need for targeted training programs to address these deficiencies, particularly in temperature monitoring and understanding vaccine availability, to ensure optimal vaccine management practices and improve immunization coverage in health facilities (Tables 3-5).

Table 3: Participants' knowledge on Effective Vaccine Management (EVM).

Participants knowledge on EVM (n=52)	Knowledgeable		Lack of knowledge	
	F	%	F	%
VVM: I have the knowledge of vaccine vial monitor	36	69	16	31
Availability of vaccine: I knew the importance of availability of vaccine in the health facility	29	46	23	44
Vaccine forecasting: I knew how to forecast the vaccine requirement of health facility	44	85	8	15
MDVP policy: I have the knowledge of multi-dose vial policy	38	73	14	27
Temperature monitoring: I knew how to monitor and record temperature twice daily and had temperature records in their respective health facilities	27	52	25	48
CCE: I have the knowledge and understanding on the significance and function of cold chain equipment	40	77	12	23

Table 4: Descriptive statistics of the knowledge participant on the role of EVM

Participant's knowledge on the role of EVM	Mean	Standard deviation
I know the role of Vaccine Vial Monitors (VVM) to prevent heat-damaged	3.71	1.304

I know factors affecting vaccine management performance	3.29	1.460
I have the knowledge to estimate vaccine requirement	4.06	1.243
I have the knowledge that EVM reduce vaccine wastage	4.00	1.029

Table 5: Health facilities and health worker's compliance to WHO standard criteria of EVM.

Practice on EVM (n=52)	Complied		Not complied	
	F	%	F	%
Compliance to WHO criteria of EVM	22	42	30	58
Compliance to WHO criteria of vaccine storage	32	62	20	38
Compliance to WHO criteria of stock management	36	69	16	31
Compliance to WHO criteria of vaccine distribution	45	87	7	13
Compliance to WHO criteria of supportive supervision	39	75	13	25

This is particularly concerning, as maintaining the cold chain is vital for vaccine efficacy; improper temperature management can lead to vaccine spoilage and reduced immunization coverage. Studies have shown that failure to adhere to cold chain protocols significantly increases the risk of vaccine loss. Additionally, while 77% of participants understood the significance and function of Cold Chain Equipment (CCE), the relatively lower awareness of temperature monitoring highlights a critical area for improvement [9].

Empirical evidence suggests that training interventions can enhance healthcare workers' knowledge and practices regarding EVM. For instance, a study by Eriksson et al. found that targeted training improved healthcare workers' knowledge of VVM and cold chain management, leading to better vaccine handling and storage practices. Similarly, Kunjok et al. emphasized the importance of continuous education in improving EVM practices in South Sudan, suggesting that comprehensive training programs can effectively address knowledge gaps.

These findings underscore both strengths and weaknesses in the participants' knowledge of EVM. The high levels of understanding regarding vaccine forecasting and VVM usage reflect a solid foundation in essential areas that directly impact vaccine effectiveness. Conversely, the lower awareness of vaccine

availability and temperature monitoring indicates significant gaps that could compromise immunization efforts. This suggests an urgent need for targeted training programs to address these deficiencies, particularly in temperature monitoring and understanding vaccine availability. By focusing on these areas, health facilities can ensure optimal vaccine management practices, which are essential for improving immunization coverage and enhancing public health outcomes.

Furthermore, the understanding that EVM can reduce vaccine wastage was supported by a high mean score (4.00) among participants, corroborating findings from studies conducted in Ghana and Ethiopia. These studies highlighted that effective vaccine management practices are directly linked to reduced vaccine wastage and improved immunization coverage.

Overall, while the foundational knowledge exists among healthcare workers, targeted interventions are necessary to bolster their competencies in critical areas of EVM. Enhanced training and resources can help bridge the knowledge gaps, ultimately leading to more effective vaccine management and better immunization outcomes in health facilities. Addressing these gaps through structured training programs will not only improve individual knowledge but also contribute to overall public health by ensuring more effective vaccine distribution and administration.

As respondents provided responses using a five-point Likert scale, mean score analysis was conducted following the criteria that a mean score between 1.00-1.80 is considered very low, 1.81-2.60 as low, 2.61-3.20 as medium, 3.21-4.20 as high, and 4.21-5.00 as very high. The analysis of participants' knowledge on Effective Vaccine Management (EVM) reveals a nuanced understanding of various critical aspects, as demonstrated by their responses on a five-point Likert scale. The mean scores indicate that knowledge levels vary significantly across different areas, with the knowledge of Vaccine Vial Monitors (VVM) scoring 3.71, reflecting a moderate understanding of its role in preventing heat damage. This aligns with findings from Eriksson et al., who emphasize the importance of VVM in maintaining vaccine efficacy in challenging environments.

The participants' high mean score of 4.06 for estimating vaccine requirements suggests a solid grasp of this essential aspect of EVM. This is crucial, as accurate forecasting directly influences vaccination coverage and reduces waste. Conversely, the lower mean score of 3.29 regarding factors affecting vaccine management performance highlights an area needing attention. This aligns with Osei et al., who found that inadequate understanding of various factors can lead to inefficiencies in vaccine management practices.

Additionally, the strong awareness of EVM's role in reducing vaccine wastage, with a mean score of 4.00, indicates that participants recognize the importance of effective practices. However, the variability in responses, as shown by the standard deviations, points to inconsistent knowledge among participants, which suggests a need for targeted training programs. Such interventions could focus on bridging knowledge gaps, particularly regarding factors affecting vaccine management, to enhance overall EVM practices. Overall, while the findings indicate a positive foundation of knowledge among healthcare workers, they underscore the necessity for ongoing education and training to strengthen EVM understanding and practices in health facilities. By addressing these gaps, health authorities can improve immunization outcomes and ensure the effective management of vaccines in their care.

Health facilities and health workers compliance to who standard criteria of effective vaccine management

The assessment of Effective Vaccine Management (EVM) practices among 52 participants revealed significant variability in compliance with WHO standards. Overall, only 42% of participants met the general EVM criteria, indicating a concerning trend, as the majority (58%) failed to adhere to the established guidelines. Specific compliance rates showed that 62% of participants followed vaccine storage protocols, while stock management compliance was higher at 69%. Vaccine distribution emerged as the strongest area, with 87% adherence to guidelines, and supportive supervision practices were also

robust, with 75% compliance. Despite these strengths, the 38% of respondents who did not comply with vaccine storage guidelines raises serious concerns about the potential risk to vaccine efficacy.

These findings echo similar studies in the literature. For instance, a study by Osei et al. found that inadequate storage practices in Ghana contributed to vaccine wastage and compromised immunization efforts. Similarly, Kunjok et al. highlighted that poor compliance with storage protocols significantly impacted the efficacy of vaccines in South Sudan. These studies emphasize the critical importance of adhering to established EVM guidelines to prevent vaccine loss and ensure public health safety.

The high compliance rates in vaccine distribution and supportive supervision indicate that there are solid foundations on which to build further improvements. However, the notable gaps in vaccine storage and stock management highlight the urgency for targeted interventions. Training programs focused on these specific areas, alongside enhanced resource allocation, are essential for bridging these gaps. For instance, Eriksson et al. emphasized the need for comprehensive training for healthcare workers to enhance their understanding of EVM practices, thereby improving compliance and vaccine management outcomes.

Addressing compliance issues is crucial for ensuring effective vaccine management, which in turn will enhance immunization outcomes and contribute to overall public health protection. By prioritizing improvements in storage and management practices, health authorities can better safeguard the potency and effectiveness of vaccines, ultimately leading to more successful vaccination campaigns and better health outcomes for the populations served. Addressing these challenges will require a multifaceted approach, including investment in cold chain infrastructure and ongoing education for healthcare personnel, as underscored by Hailu et al.

Challenges of Effective Vaccine Management (EVM) practices

The assessment of challenges affecting Effective Vaccine Management (EVM) practices among 52 participants revealed significant barriers across various areas. With a mean score of 2.76 (SD=1.56) for policy-related challenges, the findings suggest that while these issues are acknowledged, they may not be the most pressing concern. Conversely, management support-related challenges scored higher at 3.63 (SD=1.42), indicating a substantial perception among participants that stronger managerial backing is essential for effective vaccine management. This aligns with findings by Osei et al., which emphasize the critical role of management in facilitating EVM practices (Table 6).

Table 6: Mean of EVM challenges of EVM.

Items: Challenges affecting EVM practice (N=52)	Number of item	Mean	Std. deviation
Policy related challenges	4	2.76	1.56
Management support related challenges	4	3.63	1.42
Cold chain equipment challenges	5	3.8	1.28
Training and supportive supervision challenges	3	3.78	1.25
Vaccine logistics management related challenges	8	3.58	1.42

Cold chain equipment challenges emerged as the most significant concern, with a mean score of 3.80 (SD=1.28). The importance of reliable cold chain equipment is well-documented in the literature, as inadequate cold storage can lead to vaccine spoilage and ineffective immunization programs. Such findings highlight the need for investments in cold chain infrastructure to ensure vaccine potency and safety.

Training and supportive supervision challenges also scored notably high at 3.78 (SD=1.25), reflecting a recognized need for enhanced training resources. This resonates with existing literature, which stresses that well-trained healthcare workers are crucial for the successful implementation of EVM practices. Insufficient training can lead to poor handling of vaccines, further exacerbating issues related to vaccine wastage and efficacy.

Vaccine logistics management-related challenges scored 3.58 (SD=1.42), indicating persistent logistical issues that complicate effective vaccine distribution. The coordination of vaccine logistics is fundamental for maintaining the cold chain and ensuring timely availability of vaccines at health facilities. Studies have shown that logistical inefficiencies can severely hinder vaccination efforts, particularly in rural and resource-limited settings.

Overall, these findings underscore the necessity of addressing these challenges to bolster EVM practices. By prioritizing improvements in cold chain infrastructure, enhancing management support, and providing robust training initiatives, health facilities can strengthen their capacity to manage vaccines effectively. This, in turn, is likely to lead to improved immunization outcomes, ultimately benefiting public health.

CONCLUSION

This study evaluated the knowledge, compliance, and challenges related to Effective Vaccine Management (EVM) among healthcare workers in Wau county. Findings revealed a mixed level of understanding among participants, with strong knowledge in areas like vaccine forecasting and the use of vaccine vial monitors, while gaps were evident in vaccine availability and temperature monitoring. This highlights the need for targeted training programs to strengthen understanding in these critical areas.

Compliance with WHO EVM standards was notably low, with only 42% of participants meeting general criteria. While vaccine distribution and supportive supervision showed higher compliance, significant non-compliance in vaccine storage raises concerns about vaccine efficacy. Addressing these gaps through focused training and better resource allocation is essential for improving immunization practices.

The study also identified challenges in EVM practices, particularly regarding cold chain equipment, management support, and training. These challenges align with existing literature emphasizing the importance of reliable infrastructure and continuous education for effective vaccine management. The findings underscore the necessity for comprehensive training initiatives and resource improvements to enhance EVM practices. By addressing the identified gaps, health facilities can ensure better vaccine efficacy, reduce wastage, and ultimately improve immunization coverage, contributing to better public health outcomes.

LIMITATIONS

This study does not include the comprehensive logistics process involve in the procurement and supply of vaccines and their products to local health facilities in Wau county. Since all vaccines are imported, it is understood that health authorities handle the logistical process at different levels. These levels are subject to further studies beyond the scope of this research. This study indorses further research which required to identify exact priorities of vaccine intervention mechanism in Wau county.

RECOMMENDATIONS

Based on the findings of this study, the following recommendations are proposed to enhance Effective Vaccine Management (EVM) in Wau county's health facilities:

Targeted training programs: Develop and implement comprehensive training initiatives focusing on critical areas identified as gaps, particularly temperature monitoring and understanding vaccine availability. Training should include practical components to reinforce theoretical knowledge.

Strengthening cold chain infrastructure: Invest in upgrading cold chain equipment to ensure proper vaccine storage and handling. Regular maintenance and monitoring of these systems

should be instituted to prevent equipment failures that could compromise vaccine efficacy.

Enhancing management support: Encourage health facility management to provide stronger support for EVM practices. This can include allocating resources for training, ensuring staff compliance with protocols, and fostering a culture of accountability and continuous improvement.

Regular compliance audits: Conduct regular assessments of EVM compliance within health facilities to identify ongoing challenges and areas for improvement. Feedback from these audits should inform future training and resource allocation.

Collaboration with stakeholders: Engage with local and international health organizations to support capacity-building efforts and share best practices in EVM. Collaborative initiatives can provide additional resources and expertise to enhance vaccine management.

Public awareness campaigns: Implement awareness campaigns to educate healthcare workers and the community about the importance of effective vaccine management and the role it plays in improving public health outcomes.

Monitoring and evaluation: Establish a robust monitoring and evaluation framework to assess the impact of training programs and interventions on EVM practices. Regularly review these evaluations to adapt strategies as needed.

By implementing these recommendations, health facilities in Wau county can significantly improve their EVM practices, leading to better vaccine management, reduced wastage, and improved immunization coverage, ultimately enhancing public health.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Prior to data collection, ethical approval letter with reference number RERB NO_37/07/2021-MOH/RERB/A38/2021 was obtained from National Ministry of Health, Directorate of Planning and M&E South Sudan, and thereafter, data were collected after seeking the personal consent from the participants. All data were treated with confidentiality.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All data used in this manuscript are available from the first author upon a reasonable request.

COMPETING INTERESTS

The author declared that there is a non-existence of competing interests.

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AUTHORS' CONTRIBUTIONS

AMA conceived the title and designed the study (design, data collection and analysis) as the main author. SM and MM contributed to the entire manuscript design, manuscript write and review and approved the final version as corresponding author, MJM revised the final draft of the manuscript. All authors have read and approved the final copy of the manuscript.

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