

The International Journal of the Royal Society of Thailand
Volume XV-2023
ISSN 1906-7879



ราชบัณฑิตยสภา

The International Journal of the Royal Society of Thailand

Volume XV-2023
ISSN 1906-7879

The International Journal of the Royal Society of Thailand Volume XV-2023

Advisor
Professor Surapol Issaragrisil, President, The Royal Society of Thailand.

Issue Editor
Professor Sasithon Pukrittayakamee, FRS(T)
Professor Sanya Sukpanichnant, AFRS(T)

Editor Board
Professor Piyanart Bunnag, FRS(T)
Professor Sukanya Sudbanthad, FRS(T)
Professor Pornsan Watanagura, FRS(T)
Assoc. Prof. Kris Chantamara, FRS(T)
Professor Srisurang Poolthupya, FRS(T)
Professor Suda Kiatkamjornwong FRS(T)
Miss Yolada Yaiprayoon, Literateur
Miss Sayamol Sangmanee, Literateur
Mr. Nadh Wisidhwatchara, Literateur

Language Editor
Dr. Thomas John Peto

Cover Design
Mrs. Siwaporn Panphoowong
Mr. Chaiyaporn Pattanarudee

The front cover is a vocabulary compiled from a survey using the program Slido (https://www.slido.com/). Words related to the Royal Society of Thailand were collected from the society fellows who attended the quarterly parliamentary meeting on September 13, 2023 at the Crown Property Bureau Headquarters, Thailand.

Foreword
The President of the Royal Society of Thailand



The International Journal of the Royal Society of Thailand (IJRSTh) is one of the official journals of the Society served as an international forum for the communication and sharing of knowledge from all major disciplines. I would like to congratulate the Journal on publishing the 2023 volume and convey my sincere appreciation to all contributing authors from the Royal Society of Thailand and other international organizations, and to the Journal editors for their diligence, dedication, and expertise. I am confident that the knowledge shared through this publication will gain more appreciation from the public and lead to further development of science and art in the region and beyond.

The Royal Society of Thailand is recognized as a leader in the field of academic excellence consisting of 3 institutions: Academy of Science, Academy of Moral and Political Sciences and Academy of Arts. The Royal Society of Thailand is the national learned institution established by King RAMA VII in 1926. The Society is responsible for the academic work of the government and is a Thai language reference center and providing intellectual resources for research, reference and education services. The Royal Society of Thailand routinely publishes academic-specific dictionary text-books of all disciplines and issued regular journals both in Thai and English.

Professor Emeritus Surapol Issaragrisil, FRS(T)

President of the Royal Society of Thailand

Editor's Note

The International Journal of the Royal Society of Thailand is a forum for different voices on the past and future of global knowledge across all academic and semi-academic disciplines. This XV volume, 2023 contains original articles contributed by experts working in Thailand and/or international. They represent renowned institutions and include the Royal Society of Thailand, Mahidol University, MORU Oxford University, Kasetsart University, Thammasat University, University of Health Sciences Lao PDR and Asian Development Bank. The published topics cover a wide range of knowledge from past, present and future academic activities. One interest issue is the trading of published works, which is a matter of concern in the intellectual community.

I sincerely thank you Professor Suraphon Issaragrisil and Professor Suraphon Wirutharat for their support and encouragement. I would like to thank the fellows and associated fellows of the Royal Society of Thailand who participated in the poll for words related to the society as depicted on the front cover of this volume. I hope that the knowledge and ideas contained in this volume will inspire further research interest. The continuing development of science, education, and art will support improvements in health and good governance in Thailand and beyond.



Professor Emeritus Sasithon Pukrittayakamee, FRS(T)

Editor, Fellow of the Royal Society of Thailand

Contents

Foreword

Editor's Note

A Potential Use of Ego-centric Co-authorship Network Analysis for Inspecting Research Misconduct: A Case Study of Thai Researchers 1

Phrutsamon Wongnak, Tanaphum Wichaita, Anuwat Wiratsudakul, Wirichada Pan-ngum

A Research Support Model for Research Capacity Building on Health Science: A Case Study in Lao PDR 21

Sasithon Pukrittayakamee, Mayfong Mayxay, Elizabeth Ashley, Kesinee Chotivanich, Sysavanh Phommachanh, Alexo Esperato

Sustaining Health Research During the COVID-19 Pandemic: Lessons from Field Sites in Rural Cambodia 34

Dysoley Lek, Bipin Adhikari, James J Callery, Rupam Tripura, Mom Ean, Moul Vanna, Nicky Almasy, Bunreth Voeurng, Phaikyeong Cheah, Kesinee Chotivanich, Thomas J Peto

The First Licensed Malaria Vaccines: From RTS,S to R21 54

Borimas Hanboonkunupakarn, Podjanee Jittamala, Kittiyod Poovorawan, Kesinee Chotivanich, Sasithon Pukrittayakamee, Watcharapong Piyaphanee, Lorenz von Seidlein

Reflection on How to Diagnose and Classify Lymphoma 66

Sanya Sukpanichnant

Revisiting Diabetic Polyneuropathy and Autonomic Neuropathy 84

Kongkiat Kulkantrakorn

"Littérature engagée" in Thailand in the Revolutionary Years from 1973 to 1976 97

Pornsan Watanangura

Training Body and Mind for the Aged 110

Wichien Laohacharoensombat

Teaching English in a VUCA World 117

Namthip Anantsupamongkul and Savika Varaporn

The Royal Society of Thailand: Celebration of the Upcoming Centenary 131

Sanya Sukpanichnant and Kesinee Chotivanich

Appendix: Submission Guide for Authors 139

A Potential Use of Ego-centric Co-authorship Network Analysis for Inspecting Research Misconduct: A Case Study of Thai Researchers

Phrutsamon Wongnak[1], Tanaphum Wichaita[1],
Anuwat Wiratsudakul[2,3], Wirichada Pan-ngum[1,4]

Abstract

Paper mills, for-profit organizations facilitating mass production of academic publications and selling authorships to researchers, have increasingly posed negative impacts on academia worldwide in recent years. In early 2023, some researchers affiliated with institutions in Thailand were exposed and identified as participants in authorship-for-sale services offered by paper mills, leading to heightened public awareness of this issue. This objective of this study was to describe authorship profiles of researchers formally identified as paper mill clients (referred to as Index Researchers) using an ego-centric network analysis approach and evaluate any distinctions from their academic circles. This study started by describing authorship profiles of Index Researchers, including characteristics of the researcher, their co-authors, and co-authorship networks, using their publication records retrieved from online publication. Additional researchers affiliated with Thailand were added using snowball sampling. Authorship profiles of these researchers were subsequently explored by principal component analysis (PCA). The results revealed that the Index Researchers were relatively early in their career with significant annual publication counts (3.1 years since the first publication with 90 articles and 5.4 years since the first publication with 65 articles). The majority of their co-authors hailed from foreign organizations (85.6% and 90.9%). A total of 120 researchers underwent PCA, revealing that most exhibited

[1] Mahidol-Oxford Tropical Medicine Research Unit (MORU), Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

[2] Department of Clinical Sciences and Public Health, Faculty of Veterinary Science, Mahidol University, Nakhon Pathom 73170, Thailand

[3] The Monitoring and Surveillance Center for Zoonotic Diseases in Wildlife and Exotic Animals, Faculty of Veterinary Science, Mahidol University, Nakhon Pathom 73170, Thailand

[4] Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Correspondence to Wirichada Pan-ngum (PhD), Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. E-mail: Pan@tropmedres.ac

a trend of junior researchers with less academic experience publishing fewer articles than their senior counterparts. In conclusions, Intensive paper mill clients exhibit distinct authorship profiles, detectable through descriptive analysis of their ego-centric co-authorship networks. The distinctive features in the Index Researchers' authorship profiles were the high publication counts in their early careers and notably higher proportions of co-authors from specific regions. A thorough investigation of researchers displaying such profiles serves an important initial step in addressing research misconduct and enhancing integrity within academic communities.

Keywords: authorship-for-sale; co-authorship network; research integrity; research misconduct; paper mill

Introduction

Research misconduct has become a significant issue within the academic community, taking various forms over the years. While fabrication, falsification, and plagiarism, collectively referred to as FFP, are widely recognized and documented in countries with policies addressing research misconduct, less than 60% of these nations have reported other forms of misconduct (Resnik et al, 2015). In recent years, systematic misconduct has emerged in the form of for-profit organizations known as paper mills, posing a challenge to academic integrity. These paper mills mass-produce publications and sell authorships to researchers seeking publication in peer-reviewed journals. Publications from paper mills involve a variety of unethical practices, such as FFP misconduct, false authorships, and the establishment of citation rings (Candal-Pedreira et al, 2022).

In academia, researchers often face substantial pressures stemming from multiple factors. These include the drive to achieve career advancement rewards, such as enhancing their reputation and elevating authorship metrics like the h-index (Teixeira Da Silva, 2021). At the same time, researchers may hold significant concerns about facing potential consequences if they fail to meet the academic expectations established by their respective affiliated institutions. Under these pressures, some researchers may have become embroiled in authorship-for-sale services offered by paper mills, with Thailand being no exception.

In 2022, two researchers affiliated with different organizations in Thailand were featured in online blog posts that presented evidence of their involvement in paper mill service activities (Schneider, 2022; Wise, 2022). Subsequently, concerns about the transparency of some of their articles, including issues related to reproducibility, result fabrications, and collaborations among co-authors from diverse academic domains, were raised on PubPeer forums (https://pubpeer.com/). The compilation of this evidence has resulted in the retraction of several of their articles and has also sparked heightened public attention and awareness regarding research integrity within the broader community in Thailand. Later in 2023, their involvement with paper mill services of these researchers, along with some additional researchers, were confirmed following formal investigations by the ethical committees of their respective organizations. This emerging issue highlights the need for tools to detect and address research misconduct within the academic community, particularly in Thailand.

Social network analysis is a versatile tool for exploring entity relationships, applicable across various domains. It has been used to explore collaborative networks among institutions, countries, or regions, pinpointing influential knowledge drivers in specific fields (Fonseca et al, 2016). Further, ego-centric network analysis, a subset of social network analysis that examines partial networks centered around a single individual (referred to as 'ego'), has also been used to examine co-authorship patterns and assess the performance of individual researchers (Abbasi et al, 2012). With the proliferation of paper mill activities in recent years, the true collaborative network patterns among academic entities may have become obscured by the presence of false co-authorships from these activities. Yet, it is reasonable to expect that extensive use of such services can create a distinct authorship profile distinguishable through a network analysis approach.

The objective of this study was to utilize ego-centric network analysis to examine the various authorship profiles of researchers formally identified as clients of paper mill services and assess how they differ, if at all, from other researchers within their academic circles. These distinct profiles could potentially serve as indicators for identifying misconduct activities. Our focus was on the Thai research community, presented as a case study with potential applicability to broader contexts.

Materials and Methods

This article started by describing the co-authorship network of Thai researchers who had been confirmed to buy authorships from paper mill services, which we referred to as Index Researchers (IR_01 and IR_02). Then, we expanded our analysis to include the co-authorship networks of additional researchers, affiliated with an organization in Thailand, using a snowball sampling method. We subsequently described if false authorships of these Index Researchers exhibited any distinct characteristics compared to those of other researchers. All the analyses in this study were performed using R programming language version 4.3.0 (R Core Team, 2022).

Publication records

We obtained full publication records for individual researchers from the Dimensions Publication database (https://app.dimensions.ai/discover/publication), which were subsequently utilized in the network analysis of each researcher's co-authorship. The dataset comprises the following details: article titles, corresponding digital object identifiers (DOIs), publication dates, author lists with their respective affiliations and countries, journal names, and the domains of research covered by each journal, classified according to the Australian and New Zealand Standard Research Classification (ANZSRC) 2020 (Australian Beureau of Statistics, 2020).

We restricted our subsequent analyses to articles published before January 31, 2023, to mitigate the potential impact of altered publication patterns following the increased awareness of research integrity after January. Additionally, our analyses focused solely on original articles published in academic journals published in English language, excluding theses, preprints, corrigenda, and retraction notes.

Snowball sampling

As this study aimed to explore the potential distinctions in publication record profiles and co-authorship network characteristics between Index Researchers and other Thai-affiliated researchers, we extended our investigation of publication records to the latter group through a snowball sampling method.

Briefly, we started our investigation by examining the publication records of Index Researcher IR_01, who demonstrated a higher maximum annual publication count than Index Researcher IR_02. Initially, we identified the frequent co-authors of Index Researcher IR_01, comprising the top 15% of frequently co-published authors.

If the number of these frequent co-authors exceeded 10, we included only the top 10 frequent co-authors. In addition, frequent co-authors who do not affiliate with an organization in Thailand, as well as those who have co-authored fewer than 3 articles, were excluded. Subsequently, publication records of the remaining frequent co-authors of the Index Researcher IR_01, regarded as Researchers in Circle 1 (RC_1), were retrieved from the database for further analyses. The snowball sampling process was iterated for all members of RC_1 to incorporate their frequent co-authors into Circle 2 (RC_2), and this process continued until we reached Researchers in Circle 4 (RC_4).

Characteristics of co-authorship networks

Publication records of each included individual researcher were employed to establish a weighted, ego-centric co-authorship network, using *igraph* package (Csardi & Nepusz, 2006). Given the significant impact of paper mills on the academic community in recent years (Abalkina, 2022), we restricted our analysis to publication records from the past five years, spanning from January 31, 2018, to January 31, 2023. Additionally, we restricted our analysis to publications with fewer than 25 co-authors to emphasize co-authorships characterized by relatively equal contributions, as opposed to those with a larger number of co-authors.

In the co-authorship network of each researcher (ego), nodes represented co-authors (alters) of the ego. Edges in the network were non-directional and indicated that two researchers had collaborated on an article, with the weight of the edges determined by the number of articles they co-authored. Publication record profiles of each researcher were subsequently described using three following categories: 1) Researcher (ego) characteristics; 2) Co-author (alters) characteristics; and 3) Ego-centric co-authorship network characteristics.

Firstly, researcher characteristics encompassed the following variables: 1) Time since the first publication (in years), reflecting their experience in their research career; 2) Average annual publication count over the past 5 years; 3) Maximum annual publication count over the past 5 years; 4) Proportions of published articles categorized as review articles, systematic review articles, or meta-analysis articles; and 5) Diversity of ANZSRC 2020 research domains, calculated using Shannon's index of diversity (entropy) (Shannon, 1948).

The characteristics of co-authors were described as proportions of the geographical subregions of their respective countries of affiliation, calculated as a ratio to the total number of co-authors. The geographical subregions were classified following the M49

standard established by the United Nations Statistics Division (available at: https://unstats.un.org/unsd/methodology/m49/). Furthermore, as this article exclusively focuses on researchers with Thai affiliations, we excluded Thailand from the South-eastern subregions when calculating the proportions.

Finally, the characteristics of co-authorship networks were described using the following variables: 1) Number of co-authors (network size); 2) Edge density, calculated as the ratio of the number of edges to the total number of all possible edges; 3) Number of communities, classified using the greedy optimization of modularity algorithm; and 4) Clustering coefficient (transitivity), representing the probability that the adjacent researchers of a researcher have co-authored an article.

Statistical analyses

Monotonic relationships among the characteristics of researchers, their co-authors, and networks was assessed by computing pairwise Spearman's correlation coefficient . Subsequently, the principal component analysis (PCA) was performed on the centered and normalized values of each variable to reduce the dimensions of highly correlated characteristics among all researchers and identify variables that explain most of the variations. In the PCA, we included only the proportions of geographical subregions for most co-authors of Index Researchers IR_01 and IR_02, which encompassed Thailand, Non-Thailand South-eastern Asia, Southern Asia, and Western Asia. Additionally, given the suggestion that paper mill services are primarily based in Eastern Europe (Abalkina A, 2021), we also incorporated the proportion of co-authors from Eastern Europe into the analysis. The PCA was conducted using the *FactoMineR* (Lê et al, 2008) and *factoextra* (Kassambara & Mundt, 2020) packages.

As the final part of this case study, we further examined the detailed characteristics of the co-author networks of two groups of researcher, each comprising three researchers: 1) High-performance junior researchers (HJRs), defined as researchers with the lowest Euclidean distance from the coordinates of Index Researcher IR_01 on the first two dimensions of the individual PCA plane; 2) Senior researchers (SRs), defined as researchers who showed the most alignment on the same dimension and direction with the variable "time since the first publication".

Results

Authorship profiles of Index Researchers

Both Index Researchers, IR_01 and IR_02, are relatively early in their academic careers, with time-since-first-publication durations of 3.1 and 5.4 years, respectively (Figures 1A & 2A). Over the past five years, both IR_01 and IR_02 have published a cumulative total of over 100 articles each, with a maximum of 90 articles for IR_01 and 65 for IR_02 in a single year. The number of articles published by both researchers in 2021 underwent a substantial increase compared to the previous year. Furthermore, the diversity index of their research domains was relatively high, exceeding 3.0. Additionally, a notable proportion of their articles consisted of either review articles, systematic review articles, or meta-analyses (Figures 1A & 2A).

In the three years since their first publication, Index Researcher IR_01 has collaborated with 480 co-authors, resulting in a total of 29 communities (research groups) as classified using the greedy optimization of modularity algorithm (Figure 1B). Meanwhile, Index Researcher IR_02 has a total of 20 communities, consisting of 426 co-authors (Figure 2B). Besides, both co-author networks exhibit low clustering coefficients.

While both researchers are affiliated with Thai organizations, the majority of their co-authors, at 85.6% for IR_01 and 90.9% for IR_02, are affiliated with foreign organizations (Figures 1C & 2C). Most co-authors for both Index Researchers have affiliations in Western Asia (IR_01: 21.7%; IR_02: 20.9%), Southern Asia (IR_01: 26.8%; IR_02: 19.7%), and non-Thailand Southeastern Asia (IR_01: 11.7%; IR_02: 20.9%). Meanwhile, the proportions of co-authors from Eastern Europe were 9.2% and 8.7% for IR_01 and IR_02, respectively.

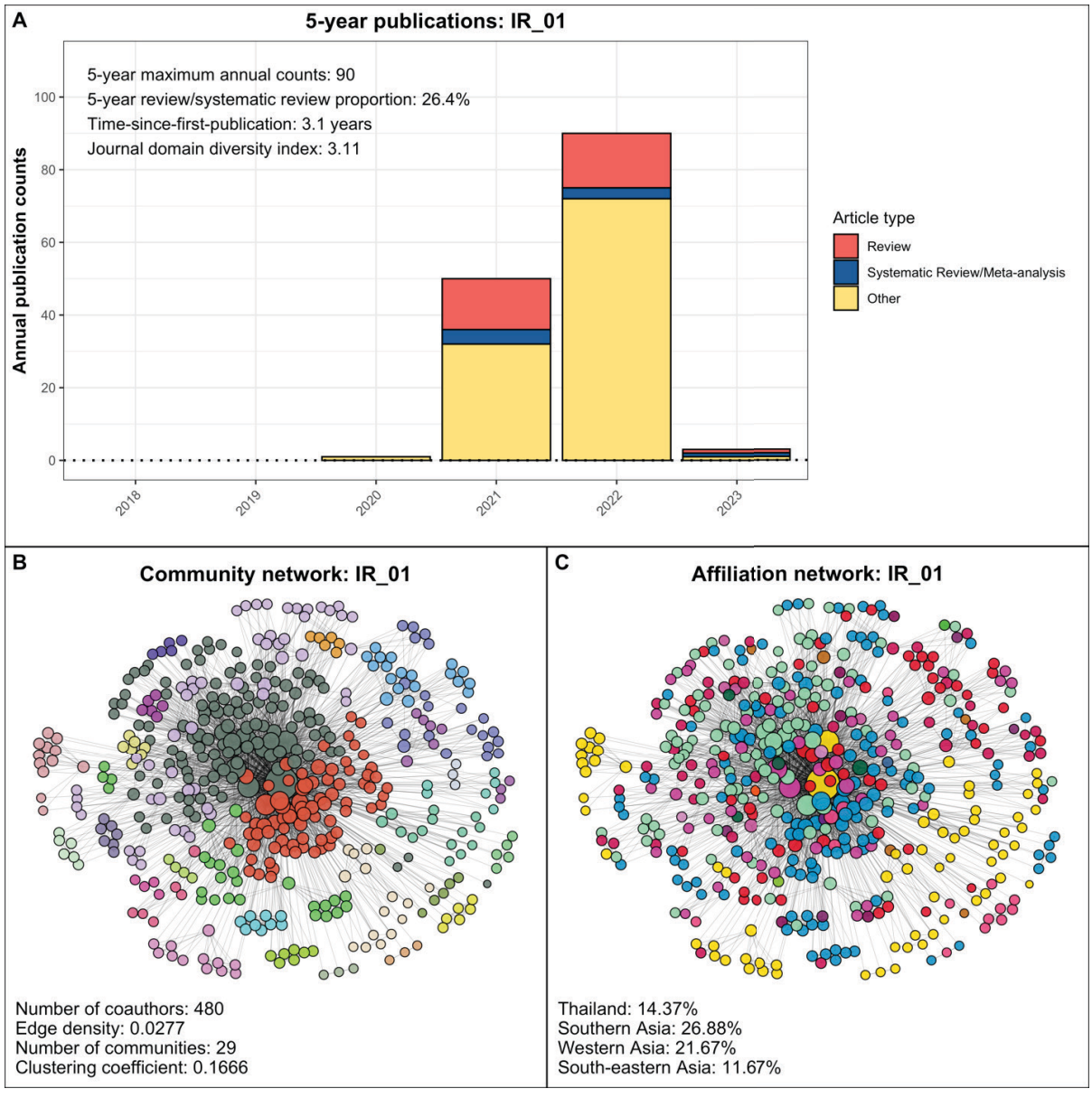


Figure 1 Authorship profiles of index researcher IR_01: A) Annual publication counts during recent 5 years (2018 to 2023), highlighted by types of articles (review article, systematic review/meta-analysis articles, or other article types); B) Communities within the co-authorship network, indicated by colors; C) Geographical subregions of coauthors' affiliations within the co-authorship network, indicated by colors. Researchers with an affiliation in Thailand are represented by yellow nodes. Nodes and edges of the network represent individual researchers and their co-authorships, respectively. Edge width represent the strength of co-authorship between two researchers, indicated by number of articles they have co-authored.

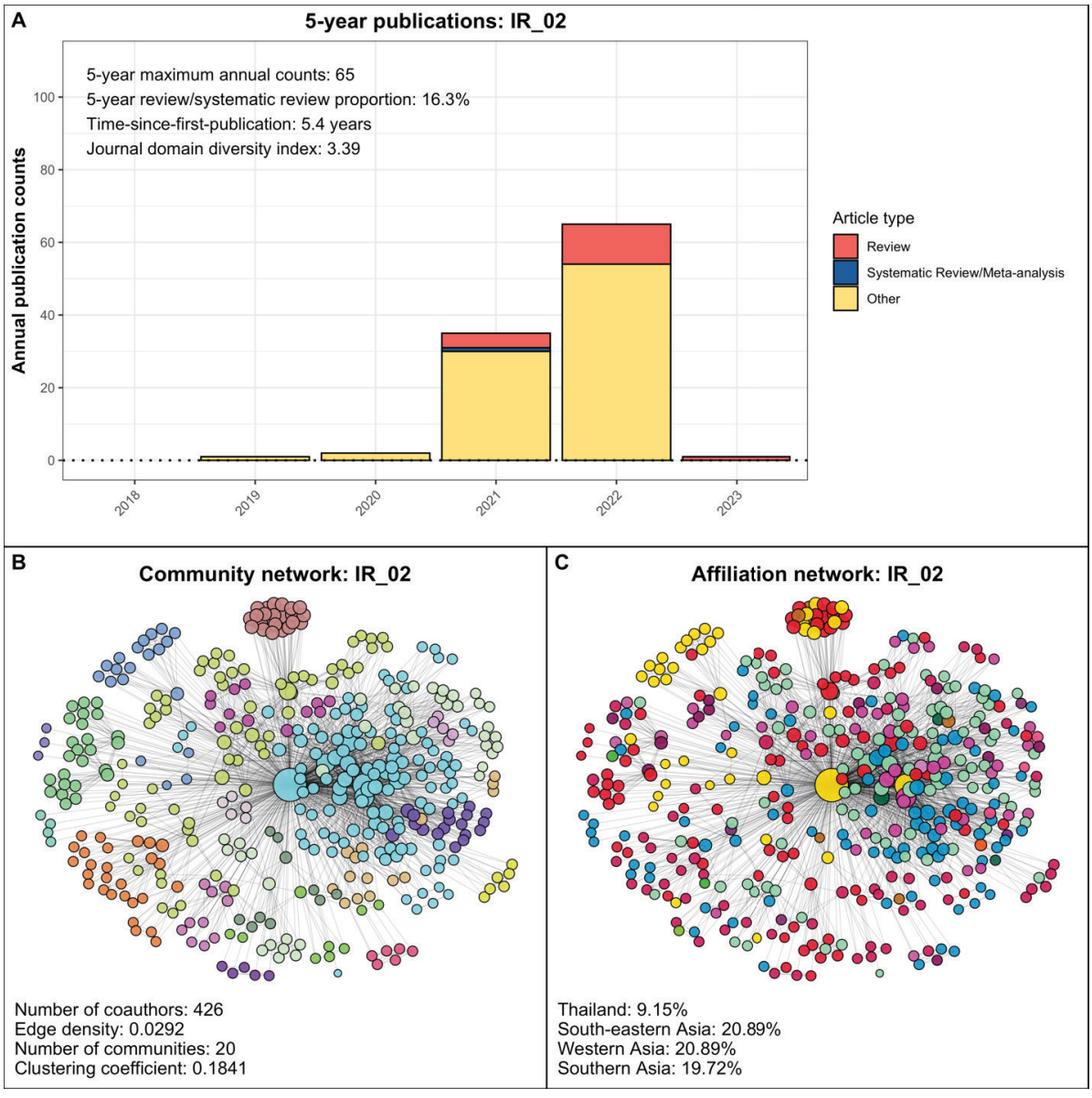


Figure 2 Authorship profiles of index researcher IR_02: A) Annual publication counts during recent 5 years (2018 to 2023), highlighted by types of articles (review article, systematic review/meta-analysis articles, or other article types); B) Communities within the co-authorship network, indicated by colors; C) Geographical subregions of coauthors' affiliations within the co-authorship network, indicated by colors. Researchers with an affiliation in Thailand are represented by yellow nodes. Nodes and edges of the network represent individual researchers and their co-authorships, respectively. Edge width represent the strength of co-authorship between two researchers, indicated by number of articles they have co-authored.

Authorship profiles of researchers affiliated with Thai organizations

Based on the snowball sampling, a total of 120 researchers, affiliated with Thai organizations from Circles 1 to 4 of IR_01, were included in subsequent principal component analysis. The first two PCA dimensions explained a total of 58.8% of the total variation among the included researchers (Figures 3 & S1).

The primary driver of the first PCA dimension was the maximum and average number of publications in the past 5 years, followed by the number of research communities and the proportions of co-authors with affiliations in Western Asia and Thailand, respectively (Figures 3A & S1). Notably, the proportion of co-authors with Thai affiliations exhibited a negative correlation with the other drivers of PCA Dimension 1 (Figures 3A & S2). At the same time, the second PCA Dimension primarily differentiated the authorship profiles of the included researchers based on the time since their first publication (academic experience), followed by the diversity of research domains and the proportions of co-authors with affiliations in Western Asia and Southern Asia, respectively. (Figures 3A & S1). While the clustering coefficient exhibited a negative correlation with both the maximum and average annual publication numbers, as well as the number of research communities (Figures 3A & S2).

The projections of individual researchers onto the first two PCA dimensions revealed that the majority of included researchers aligned from the upper-left quadrant (representing junior researchers with a small number of published articles) to the lower-right quadrant (indicating Senior Researchers (SRs) with a larger number of articles) on the individual PCA plane (Figure 3B). The authorship profile of Index Researchers IR_01 and IR_02 was notably distinct from that of most included researchers, as indicated by their highest coordinates in both dimensions, placing them in the upper-right quadrant (Figure 3B). This quadrant represents junior researchers with many published articles, and we will refer to them hereafter as High-performance Junior Researchers (HJRs). The detailed authorship profiles of three selected High-performance Junior Researchers (HJR_01, HJR_02, and HJR_03) and three Senior Researchers (SR_01, SR_02, SR_03) are shown in Figures S3 and S4, respectively.

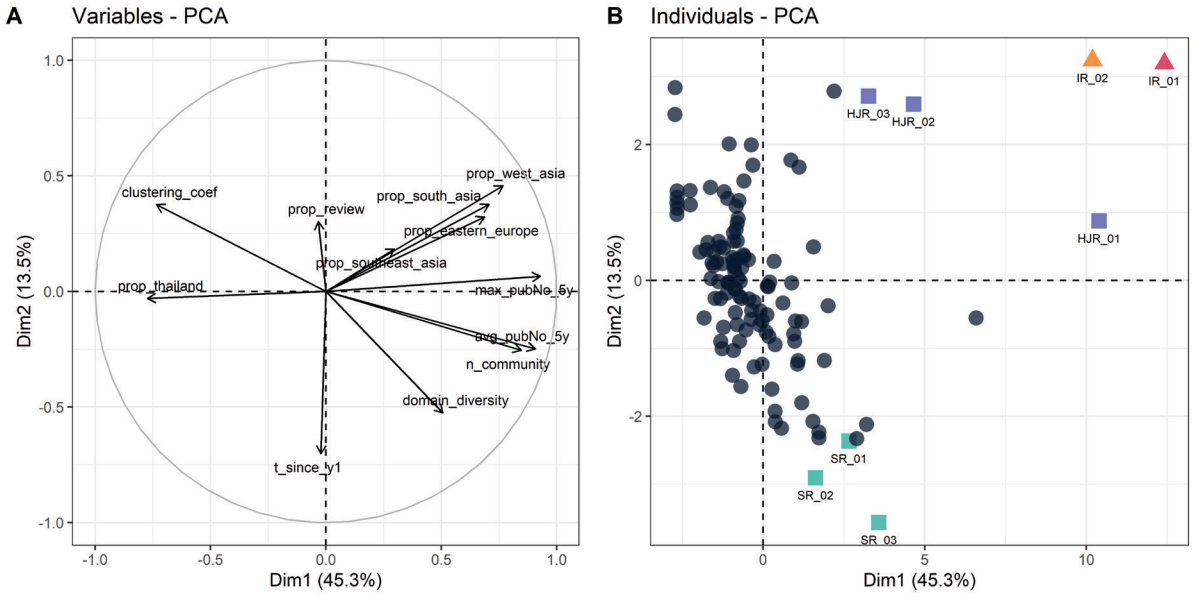


Figure 3 Principal Component Analysis (PCA) of ego, alter, and co-authorship network characteristics of researchers affiliated with an organization in Thailand. A total of 120 researchers were included in this analysis, derived from the 1st to the 4th social cycles of the index researcher IR_01 using snowball sampling. A) PCA plot for ego characteristics (time since the first publication, average annual publication number during the past 5 years, journal domain diversity, and proportion of review/systematic review articles), alter characteristics (proportions of co-authors affiliated with an organization in Thailand, non-Thailand South-eastern Asia, Southern Asia, Western Asia and Eastern Europe), and co-authorship network characteristics (number of co-authors during the past 5 years, edge density, number of communities, and clustering coefficient). B) PCA plot for individual researchers. Most researchers included in the analysis are represented by black circles, with the red and yellow triangles indicating index researchers IR_01 and IR_02, respectively. Blue squares indicate high-performance junior researchers (HJR_01, HJR_02, and HJR_03) with the smallest Euclidean distance to the index researcher IR_01 on the plane of the first two PCA dimensions. Green squares represent senior researchers (SR_01, SR_02, and SR_03) with the lowest coordinates on the second dimension. Details of abbreviations in Panel A were shown in Table S1.

Among all the researchers included, the most distinctive feature of the authorship profiles of both Index Researchers was their noticeably higher proportion of co-authors from Eastern Europe, exceeding 7.5%, while other researchers had less than 1.25% (Figure 4J). While the authorship profiles that distinguished both Index Researchers and High-performance Junior Researchers from Senior Researchers were the proportions of co-authors from Southern Asia (Figure 4H) and Western Asia (Figure 4I). In contrast, differentiating Index Researchers and Senior Researchers based on other authorship profile aspects, such as the structures of co-authorship networks (number of communities and clustering coefficient) (Figures 4E & 4F), proportions of review articles (Figure 4D), or the diversity of research domains (Figure 4G), turned out to be challenging.

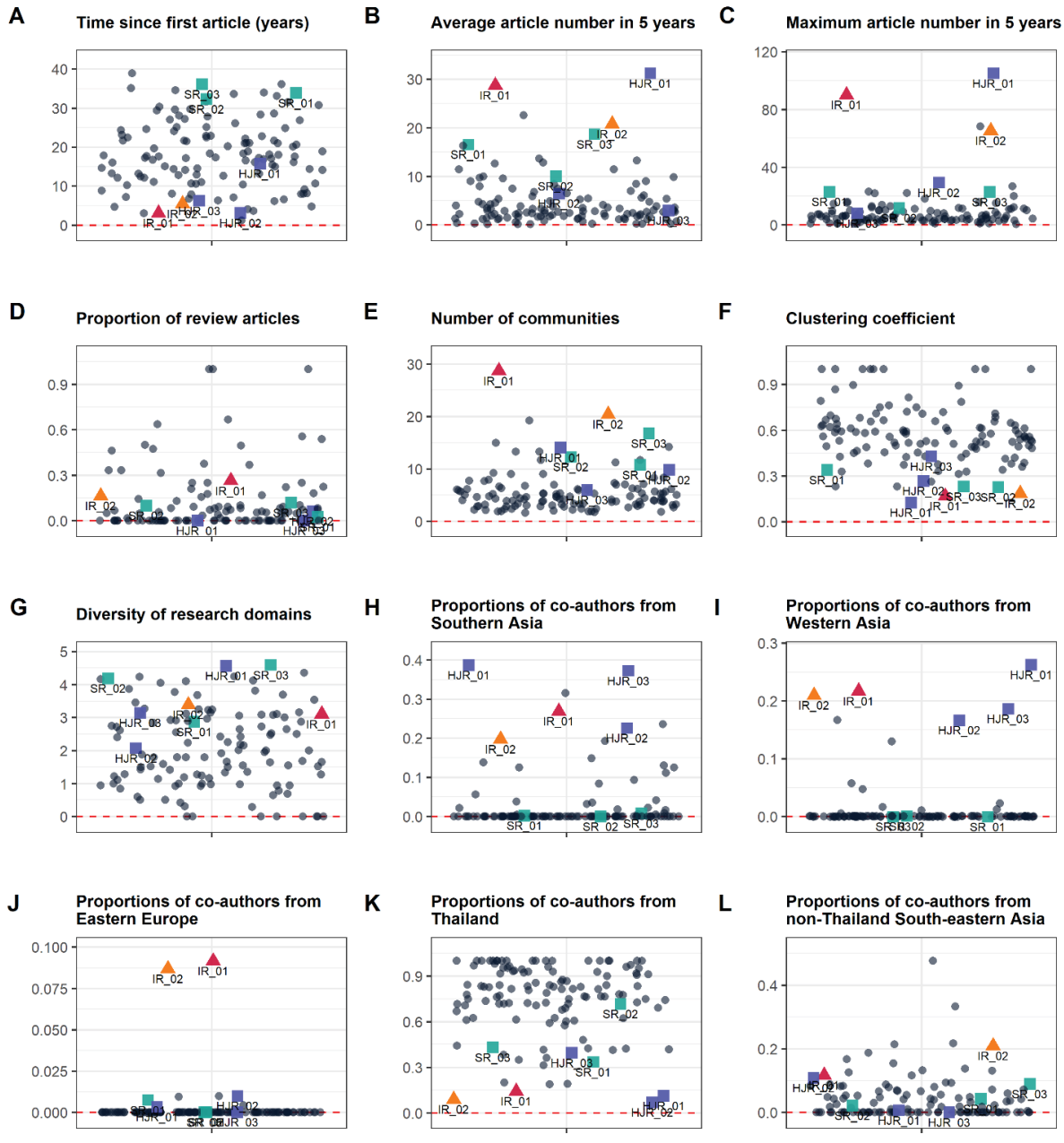


Figure 4 Stripcharts illustrating the authorhsip profiles of the 120 researchers included in this study. Index Researchers (IR_01) and (IR_02), High-performance Junior Researchers (HJR_01, HJR_02, HJR_03), and Senior Researchers (SR_01, SR_02, SR_03) are denoted by red triangles, orange triangles, blue squares, and green squares, respectively. Horizontal coordinates have been spread out for enhanced visibility.

Discussion

Paper mill services have increasingly impacted academic communities globally in recent years, giving rise to various forms of research misconduct, including authorship-for-sale, data fabrication, fake peer review, and citation rings (Christopher, 2021). In this study, we illustrate how the authorship profiles and co-authorship networks of researchers involved in authorship-for-sale activities through paper mill services may differ from those of other researchers in their academic circles within the context of Thailand.

Among the 120 researchers in our analysis, authorship profiles generally followed a trend where junior researchers, with less academic experience, published fewer articles compared to their senior counterparts. Whereas both Index Researchers and some other High-Performance Junior Researchers deviated from this trend by publishing a substantial number of articles. For instance, High-Performance Junior Researcher HJR_01 has published up to 105 articles in a year. Our findings were in line with previous reports suggesting that paper mill services primarily operate in certain countries in Eastern Europe, Western Asia, and Southern Asia (Abalkina, 2022; Christopher, 2021; Patnaik, 2016; Stone, 2016), as reflected by the high proportions of co-authors on Index Researchers from these regions.

While High-Performance Junior Researchers exhibited proportions of co-authors from Western Asia and Southern Asia similar to those of Index Researchers, their proportion of co-authors from Eastern Europe was notably lower. Interestingly, unblinding the identity of HJR_01 revealed that this researcher had also been confirmed to be involved with paper mill by the integrity committee of his/her affiliated organization, despite having some dissimilar authorship profiles from the two Index Researchers. This compilation of evidence suggested that Index Researchers and HJR_01 may have been involved with separate paper mill service platforms operating in different countries or regions.

Our study demonstrates that quantitative analysis techniques applied to researchers' authorship profiles can identify distinctive profiles that raise suspicions of research misconduct involvement. However, these techniques are effective when profiles show clear signals, such as unusually high annual publication counts early in one's career. Moreover, certain authorship profile indicators used to identify suspicious researchers, such as the proportions of co-authors from specific regions, may be unique to Thailand's academic communities. Consequently, it is not advisable to directly generalize the suspicious authorship profiles suggested by our study as the definitive method for confirming if individual researchers have purchased authorship from

paper mill services, especially in the contexts of other countries. Rather, our criteria could be used as a screening method that could support further investigation of research misconduct activities.

We acknowledge some technical limitations in our study. Firstly, we relied on data from a single database, which could have led to the exclusion of certain researchers. Secondly, our analysis depended on lexical matches of researchers' names, potentially introducing errors. This approach treated distinct researchers sharing the same first and last names as identical individuals. Additionally, variations in the spelling of researchers' names were considered as separate individuals.

In conclusion, our co-authorship network analysis provides insights into authorship profiles associated with authorship-for-sale activities, laying the groundwork for further investigations into various types of misconduct. To effectively combat systematic research misconduct, we propose the following future approaches: 1) Identifying and tracking researchers who belong to the same communities, classified by network analysis algorithms, as researchers confirmed to have purchased their authorships; 2) Incorporating machine learning algorithms on a larger sample size to identify suspicious researchers more accurately; 3) Analyzing citation networks to gain a deeper understanding of the patterns of citation rings, which are often associated with paper mill activities; 4) Analyzing aggregated co-author networks of suspicious researchers to identify the key individuals who facilitate paper mill activities within academic communities.

Conclusion

Authorship-for-sale is a form of various research misconducts facilitated by paper mill service platforms that poses negative impacts on academic communities. Through intensive use of these services, distinct authorship profiles of such researchers become evident through descriptive analysis. In the context of the academic community in Thailand, we observed that suspicious researchers may accumulate a substantial number of publications early in their careers. Additionally, a significant proportion of their co-authors may be affiliated with regions where paper mill platforms operate. Thoroughly investigating such suspicious researchers serves as an important initial step in combating systemic research misconducts and improving integrity within academic communities.

Data availability

The data that support the findings of this study are openly available at https://github.com/psamonwong/CoauthorshipNetwork.

About the authors

Phrutsamon Wongnak is currently affiliated with the Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University. His research interests are in veterinary epidemiology and disease ecology using computational methods, including statistical and mathematical modeling.

Tanaphum Wichaita is a research software engineer in the Mathematical And Economic MODelling (MAEMOD), the Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University. He supports the research of the group by developing model codes and tools for communicating and maximizing model usage by primarily using the R language. He also builds web applications by using Shiny package, HTML and CSS.

Anuwat Wiratsudakul is an Associate Professor working at the Department of Clinical Sciences and Public Health, Faculty of Veterinary Science, Mahidol University. His research covers different aspects of infectious disease epidemiology, especially on zoonoses.

Wirichada Pan-ngum is a senior modeler leading the Mathematical And Economic MODelling (MAEMOD) at the Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University. Her interest is in neglected tropical disease modeling. She intends to use modeling as a tool to guide health policy decisions in the region and expand the network of modelers in the tropics.

References

Abalkina A. Publication and collaboration anomalies in academic papers originating from a paper mill: evidence from a Russia-based paper mill. 2022 Mar 20. [cited 2023 Sep 15] https://doi.org/10.48550/arXiv.2112.13322.

Abbasi A, Chung KSK, Hossain L. Egocentric analysis of co-authorship network structure, position and performance. Inf Process Manag 2012; 48: 671-679. https://doi.org/10.1016/j.ipm.2011.09.001.

Australian Beureau of Statistics. ANZSRC 2020 FoR - structure, definitions and explanatory notes. 2020 Jun 30 [cited 2023 Sep 15] https://www.abs.gov.au/

statistics/classifications/australian-and-new-zealand-standard-research-classification-anzsrc/2020/anzsrc2020_for.xlsx.

Candal-Pedreira C, Ross JS, Ruano-Ravina A, Egilman DS, Fernández E, Pérez-Ríos M. Retracted papers originating from paper mills: cross sectional study. BMJ 2022; e071517. https://doi.org/10.1136/bmj-2022-071517.

Christopher J. The raw truth about paper mills. FEBS Lett 2021; 595: 1751-1757. https://doi.org/10.1002/1873-3468.14143.

Csardi G, Nepusz T. The igraph software package for complex network research. InterJournal Complex Syst 2006; 1695: 1-9.

Fonseca BDPFE, Sampaio RB, Fonseca MVDA, Zicker F. Co-authorship network analysis in health research: method and potential use. Health Res Policy Syst 2016; 14: 34. https://doi.org/10.1186/s12961-016-0104-5.

Kassambara A, Mundt F. Factoextra: Extract and Visualize the Results of Multivariate Data Analyses 2020. https://CRAN.R-project.org/package=factoextra.

Lê S, Josse J, Husson F. FactoMineR : An R Package for Multivariate Analysis. J Stat Softw 2008; 25. https://doi.org/10.18637/jss.v025.i01.

Patnaik PR. Scientific Misconduct in India: Causes and Perpetuation. Sci Eng Ethics 2016; 22: 1245-1249. https://doi.org/10.1007/s11948-015-9677-6.

R Core Team. R: A Language and Environment for Statistical Computing. R foundation for Statistical Computing, Vienna 2022. [cited 2023 Sep 15] https://www.R-project.org.

Resnik DB, Rasmussen LM, Kissling GE. An International Study of Research Misconduct Policies. Account Res 2015; 22: 249-266. https://doi.org/10.1080/08989621.2014.958218.

Schneider L. You will be paid US $500-800 for each paper. Better Sci 2022 Oct 24 [cited 2023 Sep 15]. https://forbetterscience.com/2022/10/24/you-will-be-paid-us-500-800-for-each-paper/.

Shannon CE. A mathematical theory of communication. Bell Syst Tech J 1948; 27: 379-423.

Stone R. In Iran, a shady market for papers flourishes. Science 2016; 353: 1197-1197. https://doi.org/10.1126/science.353.6305.1197.

Teixeira Da Silva JA. Paper mills and on-demand publishing: Risks to the integrity of journal indexing and metrics. Med J Armed Forces India 2021; 77; 119-120. https://doi.org/10.1016/j.mjafi.2020.08.003.

Wise N. The incredible collaborations of Renaissance men and women. Better Sci. 2022 Oct 19 [cite 2023 Sep 15] https://forbetterscience.com/2022/10/19/the-incredible-collaborations-of-renaissance-men-and-women.

Supplementary information

Table S1 Abbreviations for authorship profiles used throughout the article

Variable	Abbreviation
Time since first article (years)	t_since_y1
Average article number in the past 5 years	avg_pubNo_5y
Maximum article number in the past 5 years	max_pubNo_5y
Proportion of review/systematic review/meta-analysis articles	prop_review
Number of communities	n_community
Clustering coefficient	clustering_coef
Diversity of research domains	domain_diversity
Proportion of co-authors from Southern Asia	prop_south_asia
Proportion of co-authors from Western Asia	prop_west_asia
Proportion of co-authors from Eastern Europe	prop_eastern_europe
Proportion of co-authors from Thailand	prop_thailand
Proportion of co-authors from non-Thailand Southeastern Asia	prop_southeast_asia

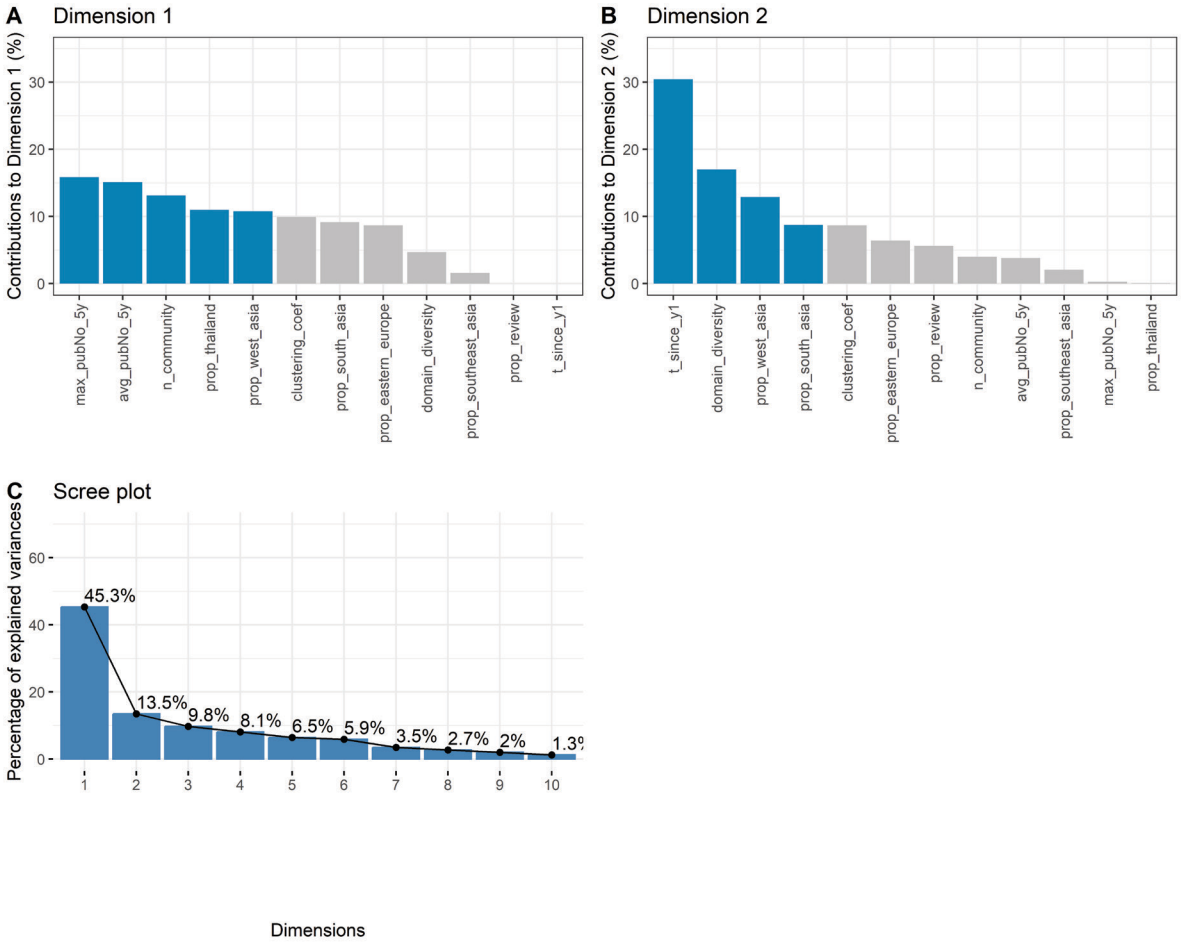


Figure S1 Contributions of ego characteristics (time since the first publication, average annual publication number during the past 5 years, research area diversity, and proportion of review/ systematic review articles), alter characteristics (diversity of sub-regions of co-authors' affiliations), and co-authorship network characteristics (network size, edge density, number of communities, and clustering coefficient) on the principal component analysis (PCA) Dimension 1 (A) and Dimension 2 (B), and the PCA scree plot (C). Details of abbreviations in Panel A were shown in Table S1.

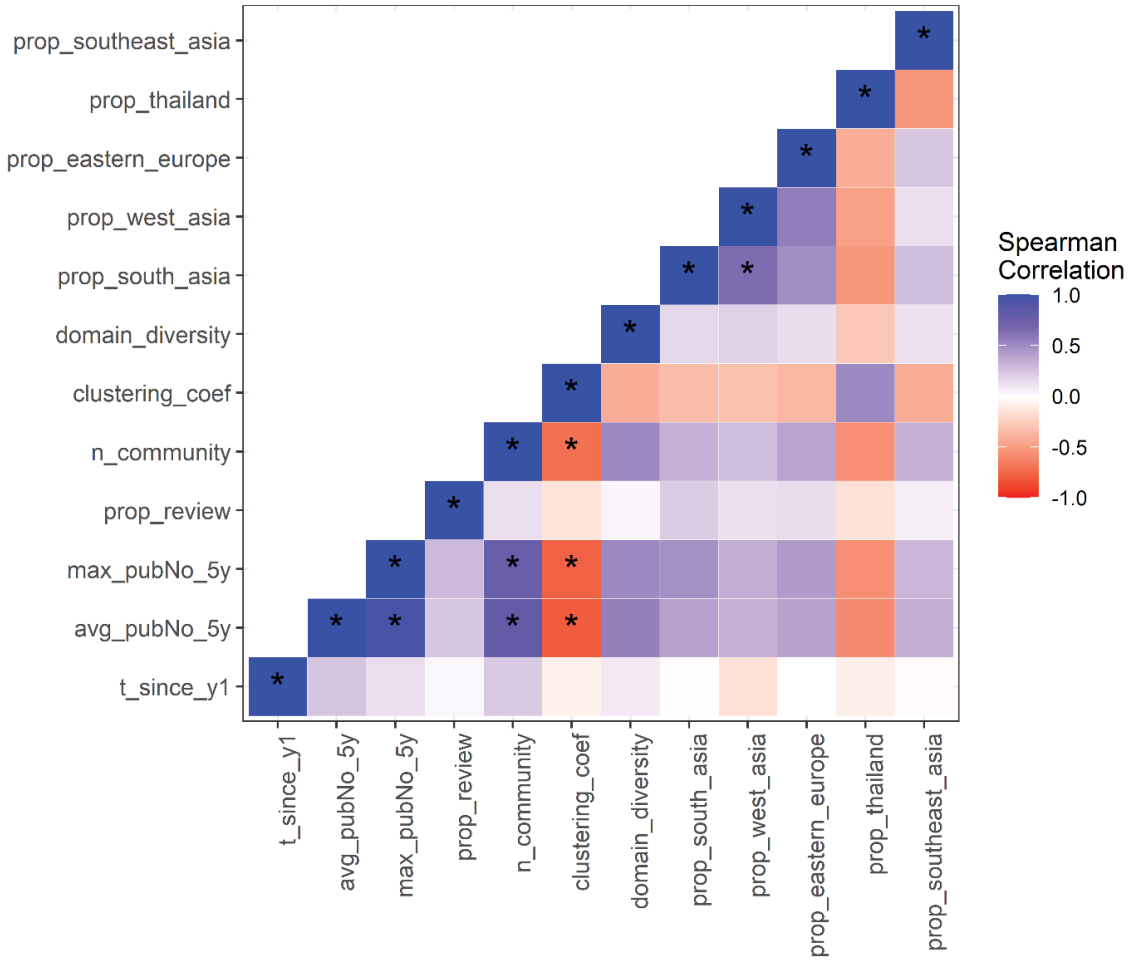


Figure S2 Pairwise Spearman's correlation coefficient of ego characteristics (time since the first publication, average annual publication number during the past 5 years, research area diversity, and proportion of review/systematic review articles), alter characteristics (diversity of sub-regions of co-authors' affiliations), and co-authorship network characteristics (network size, edge density, number of communities, and clustering coefficient). Colors indicate values of correlation coefficient (blue: = 1; white: = 0; red: = -1), with asterisks indicate > 0.6. Details of abbreviations in Panel A were shown in Table S1.

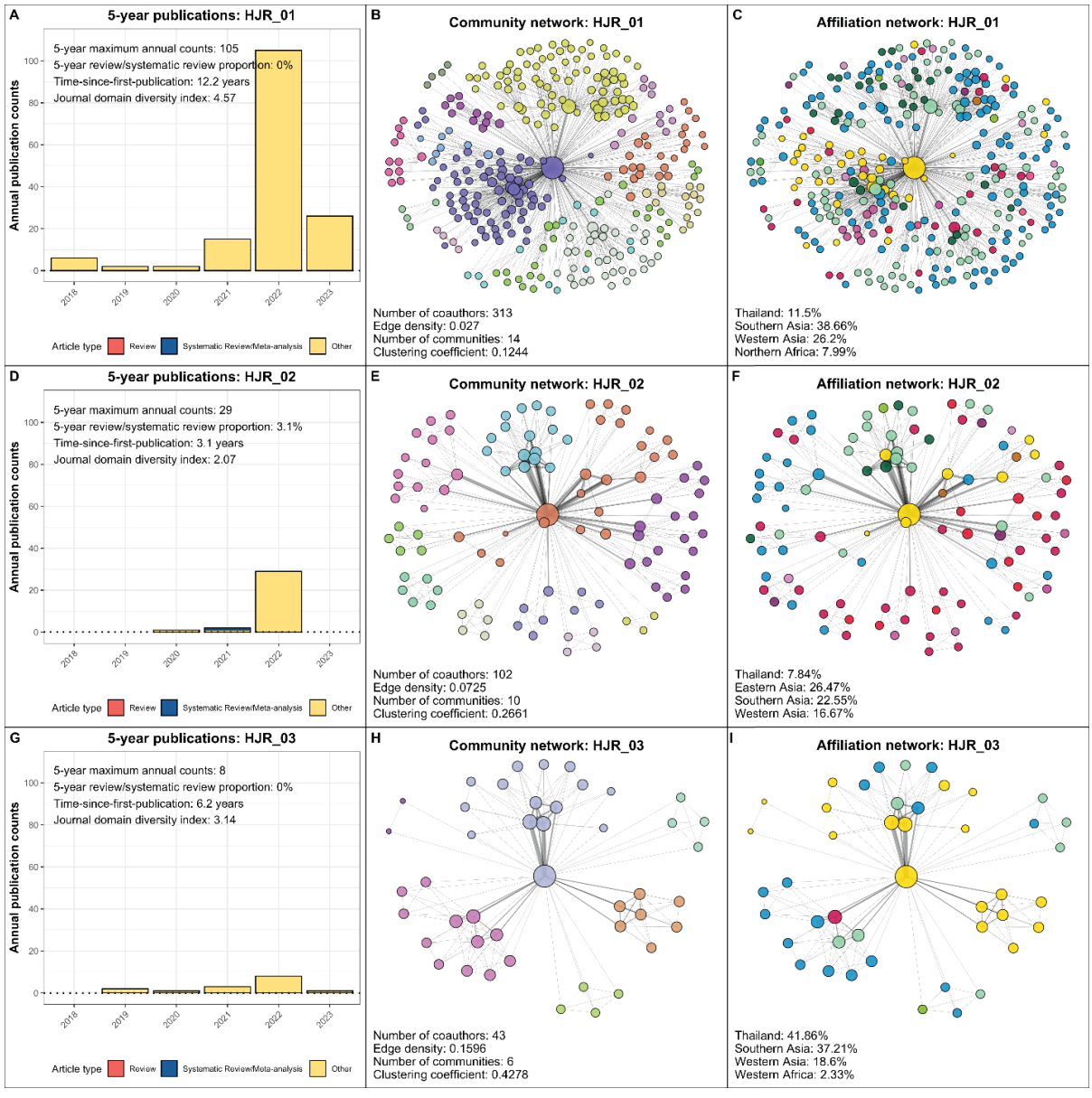


Figure S3 Authorship profiles of high-performance junior researchers HJR_01 (A to C), HJR_02 (D to F), and HJR_03 (G to I). Panels A, D and G: Annual publication counts during recent 5 years (2018 to 2023), highlighted by types of articles (review article, systematic review/meta-analysis articles, or other article types). Panels B, E, and H: Communities within the co-authorship network, indicated by colors. Panels G, H, and I: Geographical subregions of coauthors' affiliations within the co-authorship network, indicated by colors. Researchers with an affiliation in Thailand are represented by yellow nodes. Nodes and edges of the network represent individual researchers and their co-authorships, respectively. Edge width represent the strength of co-authorship between two researchers, indicated by number of articles they have co-authored.

A Research Support Model for Research Capacity Building on Health Science: A Case Study in Lao PDR

Sasithon Pukrittayakamee[1,2,3], Mayfong Mayxay[4,5,6], Elizabeth Ashley[5,6], Kesinee Chotivanich[1,2,3], Sysavanh Phommachanh[4], Alexo Esperato[7]

Abstract

A 2020-2024 project to enhance the research capacity of the University of Health Sciences (UHS), Lao PDR is currently under implementation. The project receives financial support of the Asian Development Bank (ADB), as part of a technical assistance project in collaboration with the Lao Ministry of Public Health and Mahidol University. The project has provided 300,000 USD to 44 research grant winners, which belong to 11 UHS departments and institutions. Research grants have been awarded to young (n=30) and middle-career (n=14) researchers. The grants have been awarded through a competitive research fund (CRF), which has complemented research grants with capacity building through workshops, as well as mentoring by CRF Committee members. The present article describes the characteristics of the awarded research projects and their potential impact on health services in Lao PDR. All grant recipients were successful in terms of their mid-term research outputs by June 2023. The data evaluated suggest that, when combined with capacity building, competitive research funds are a viable option to strengthen research capacity in developing countries.

Keywords: research support model; research capacity building; health science; Lao PDR; Asian Development Bank

[1] Royal Society of Thailand. Sanam Sua Pa, Dusit, Bangkok 10300 Thailand.
[2] Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.
[3] Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.
[4] Institute of Research and Education Development (IRED), University of Health Sciences, Vientiane, Lao PDR.
[5] Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU), Vientiane, Lao PDR
[6] Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

Correspondence to
Sasithon Pukrittayakamee (DPhil), Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Ratchathewi, Bangkok, 10400, Thailand. E-mail: Sasithon.puk@mahidol.ac.th
Alexo Esperato (PhD), 6 ADB Ave., Mandaluyong City 1150, Metro Manila, Philippines.
Email: aesperato@adb.org

Introduction

The Asian Development Bank (ADB) is an international donor in South East Asia. ADB is committed to achieving sustainable economic growth and extreme poverty eradication through public and private sector operations, advisory services, and knowledge support (ADB, 2017; ADB, 2023).

In alignment with Health Sector Strategy of ADB (ADB, 2017), Lao PDR is advancing towards attaining Universal Health Coverage by 2025. Quality of Health Care and medical education are essential components of the Universal Health Coverage. For these reasons, ADB has been supporting the strengthening of health professional education in Lao and other Asian countries.

The University of Health Science (UHS) is the premier medical university in Lao PDR. Since 2022, and as part of a regional technical assistance project (TA-9397-REG), ADB has been supporting the set up and implementation of a Competitive Research Fund (CRF) at UHS. This 2022- 2024 technical assistance project aims to strengthen UHS' research capacity, and is now funding 44 health research projects among faculty and students. This article describes the characteristics of the awarded research projects, and shares lessons on the set up and execution of CRFs in developing countries. The implementation of the CRF and its associated capacity building activities (mentoring and workshops) has required close collaboration from ADB as a funder and provider of technical assistance, Mahidol University as a research consultant, and UHS as a stakeholder.

Material and Methods

Competitive Research Fund (CRF)

The CRF aims to support up to 50 small and middle-scale research projects in medicine and health care delivery. Each awarded team has received a research grant of $5,000 when headed by a junior researcher and $10,000, when headed by a mid-career researcher. The grant amount is based on the quality of research, commensurate with the proposed costs. To build research capacity, grand funding has been complemented with knowledge sharing via workshops and coaching from senior researchers. Workshop sessions focus on research topics that ranged from manuscript preparation to the dissemination of research outputs. Senior researchers,

who are all members of the CRF Selection Committee, have provided regular coaching to CRF awardees through the evaluation of their proposals and progress reports, and through regular technical meetings.

The Project Team

Upon project start, ADB and UHS appointed an organization team responsible for the whole technical assistance project (Figure 1). The team comprises individuals from ADB, UHS, Lao resources, and Mahidol University.

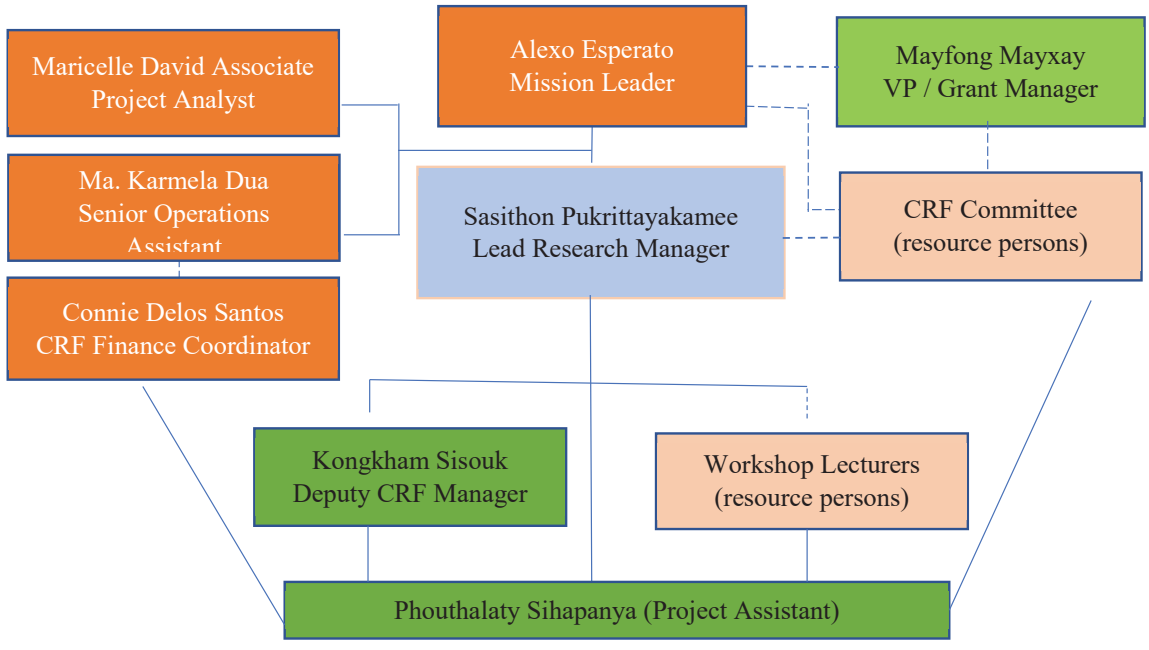


Figure 1 The CRF Project Team. A joint collaboration from ADB (orange), UHS and/or Lao PDR (green), Mahidol University (blue), and national and international experts (pink).

The CRF Project Team has coordinated CRF set up and implementation, workshops, and coaching program. This activity has required the setup of an overall CRF project plan, Standard Operating Procedures, appointment of CRF committee members, and development of project scoring sheets, and progress report templates that research awardees must abide by.

Set up and management of the Competitive Research Fund (CRF)

The CRF was designed as a vehicle to build practical capacity amongst UHS students and faculty. Its set up has been complemented by workshops on research topics and regular coaching through senior researchers. These activities have proceeded through six major stages: (1) establishment of the CRF committee, (2) organization of research workshops, (3) awarding of CRF grants, (4) CRF award contracts, (5) execution of research projects, and (6) monitoring of research projects.

(1) Establishment of CRF committee. |The CRF committee was convened at project start. It comprises 3 key personnel from the CRF Project Team, and 5 renowned Lao and international researchers, the majority of which were residents in Lao PDR. CRF committee responsibilities include reviewing and scoring CRF applications, awarding of CRF grants, mentorship of CRF awardees (5-7 awardees per 1 committee member), monitoring research projects under their mentorship, and approving the final manuscript for publications.

(2) Research workshops. CRF awards have been combined with theoretical and practical workshops. These follow a sequence throughout the 8-12 months of the roposal Development Workshop (delivered before the grants were awarded), and (B) Research Methodology Workshop, where the latter is longer and comprises four modules (study design, data analysis, manuscript writing, and dissemination of the research outputs). These four workshops were organized in 3-4 months intervals. In these workshops, CRF awardees were given opportunity to present their research progress (Figure 2).





Figure 2 Opening of training workshops on Research Proposal Development (top) and Study Design (bottom), photos taken on 2nd September 2022 and 9th January 2023, respectively

(3) Awarding of CRF grants. The grants were awarded by the CRF Committee, based on the proposals submitted by research groups. The grant selection process was based on a fair selection process, which relied on transparent selection methodology and standardized scoring sheets. The award selection process was also committed to equal opportunity for all UHS faculties, and prioritized young researchers, and research projects that explored practical solutions for pressing health challenges.

The key steps in the grant-making process include calling for proposals, reviewing the proposals, and awarding the CRF grants. The calls for proposals were distributed widely across UHS faculties, and on the ADB website. The initial call for proposals asked research teams to propose a research concept (rather than a full proposal). The CRF then selected most promising research concepts, and invited the concerned teams to develop full research proposals, with details of the research questions, methods, and data collection procedures; estimated costs, implementation and monitoring plans, milestones, and indicators. The CRF Committee then selected the proposals to be awarded based on their relevance and originality. The main criteria used for evaluating proposals included: (i) qualification, credentials, and availability of the applicants; (ii) rationale and relevance of the research objectives; (iii) innovative features; (iv) methodology. The CRF also encouraged collaboration with other research institutions and/or the private sector.

(4) CRF award contracts. Once the CRF award was confirmed by the Selection Committee, the selected research teams signed a service agreement contract with UHS and ADB, with agreed deliverables and timeline. Research teams were allocated research grants of $5,000 to $12,500. There contracts specified three grant payment milestones; 50% upon signing of the service agreement, 30% upon delivery of the first draft manuscript, and 20% upon final manuscript. The research grants were disbursed to the individual account of the principal investigator upon reaching the payment milestones.

(5) Execution of research projects. The CRF award team will execute the research projects between Q2-2023 and Q1-2024. The results section of this article summarizes the characteristics of the research projects.

(6) Monitoring of research projects. While the CRF Committee awarded the research grants and monitored the progress of the awardees, the ADB team and UHS have ensured compliance with UHS and ADB requirements. The UHS grant manager and the CRF manager were responsible for collecting updates from the research teams, and for reporting implementation progress to UHS and ADB quarterly. These updates shall also include financial progress and payment milestones.

Data analysis

The project team recorded the characteristics of research projects in Microsoft Excel spreadsheets. The team then analyzed the characteristics of projects (mean, standards deviations, and percentages) through SPSS (version 29) statistical package.

Results

The CRF awarded 44 research grants, of which 30 were assigned to young and 14 to mid-career (n=14) researchers. Grant were spread across 11 UHS departments and institutions (see Table 1). The average age (mean, standard deviation) of awardees is 37.7, 6.8 years, with a majority of awardees female (61%). The junior researchers were 5-6 years younger than the mid-career researchers (mean + SD = 35.8 +4.8 vs. 41.7 + 8.6). Thirty-two of grants (72%) were awarded to four major UHS faculties (Medicine, Public Health, Dentistry, Pharmacy) while the rest were distributed across the rest of faculties and UHS affiliated hospitals.

Table 1 CRF awardees data and their affiliations

	Junior Researchers	Mid-career researchers	Total
Numbers	30	14	44
Age (mean ± SD)	35.8 ± 4.8	41.7 ± 8.6	37.7 ± 6.8
Male:Female	10:20	7:7	17:27
No. of Institutions	7	8	11
No. of awardees by affiliations			
- Medicine	7	2	9
- Public Health	5	4	9
- Dentistry	7	1	8
- Pharmacy	6	0	6
- IRED	3	2	5
- Mahosot Hospital	0	2	2
- Medical Technology	1	0	1
- Nursing Sciences	1	0	1
- Tropical and Public Health	0	1	1
- Institute Pasteur	0	1	1
- Children Hospital	0	1	1

IRED = International Research and Education Development

Characteristics of CRF research projects.

The characteristics of the CRF projects (see Table 2) were analyzed across 5 categories: (1) Project objective, (2) Type of Research, (3) Research methodology, (4) Investigated diseases, and (5) Studies on mother and child.

As Table 2 reflects, the majority of projects focused on health service delivery or health risk assessment (n = 40; 90.9%). Over half were basic research (n = 24, 54.5 %) and the rest were of clinical (n = 7), epidemiology (n=3), and public health nature (n = 10). Project themes were spread fairly and evenly across communicable (38.6%); non-communicable (27.3%), mother-child health (36.3%) and mixed (34.1%). For data collection, most projects rely on surveys (n = 33, 75%), while the rest employ observational (n = 6), experimental (n = 3), and mixed methods (n = 2).

Table 2 Awarded CRF projects: Data are shown as numbers

	JR	MCR	No. and % of Total (n=44)
Project Objective			
• Service assessment	14	9	23 (52.2%)
• Risk assessment	12	5	17 (38.6%)
• Others	4	0	4
Research Types:	20/10	4/10	24/20
Basic/other			
Method: Survey/other	21/9	12/2	33/11
Topics by disease			
• Communicable	14	3	17 (38.6%)
• Non-communicable	9	3	12 (27.3%)
• Mixed & other	7	8	15 (34.1%)
Studied groups			
• Mother & child: no (%)	9 (30%)	7(50%)	16 (36.3%)

JR = Junior Researchers, MCR = Mid-Career Researchers

Research topics on Mother and Child group

Approximately one-third of the projects focused on maternal and child health (36.3%), particularly those from mid-career researchers (n = 7, 50%). As shown in Table 3, these sixteen mother-child projects in turn focused on dental health (n = 4), general health (n = 3), antenatal or pregnancy services (n = 2), and one project each on mental health, use of antibiotics, smoking, acute respiratory infection in children, Covid-19, diarrhea, eczema, and tuberculosis.

Table 3 Research topics of mother-child projects. Data are shown as numbers

Topics	Junior Researcher	Mid-career Researcher	Total
Dental health	3	1	4
General health	0	3	3
ANC/Pregnancy services	1	1	2
Antibiotics/AMR	1	0	1
Anxiety	1	0	1
ARI	0	1	1
Covid-19	1	0	1
Diarrhea	1	0	1
Eczema	1	0	1
Tuberculosis	0	1	1
Total	9	7	16

ANC = antenatal care, ARI = Acute Respiratory Infection, AMR = antimicrobial resistance

CRF research topics by disease group

The projects funded by the CRF have focused on more than 12 disease groups (Table 4). Covid-19 and dental health were the two most common with 13.6% each (n = 6), while general health issues made up 11.4% (n = 5). Others conditions, which accounted for 2-4 projects each, include antenatal care or pregnancy, antibiotics, dengue, tuberculosis, herb, nutrition, sexual health, and stroke. The remaining eight projects (18.1%) were the only ones to focus on their disease of interest, and covered eczema, *H.pylori*, diarrhea, nurse education, epilepsy, hepatitis B, helminths, and gender violence.

Table 4 Numbers of Specific Common CRF Topics

	JR	MCR	Total projects	Percentage of all 44 projects
Numbers of topic group	11	10	12	
Covid-19	5	1	6	13.6 %
Dental Health	5	1	6	13.6 %
General Health	0	5	5	11.4 %
ANC/Pregnancy	2	2	4	9.1 %
Antibiotics	2	1	3	6.8 %
Dengue	2	0	2	4.5 %
TB	1	1	2	4.5 %
Herb	2	0	2	4.5 %
Nutrition	1	1	2	4.5 %
Sexual Health	2	0	2	4.5 %
Stroke	1	1	2	4.5 %
Others	7	1	8	18.1 %
Total	30	14	44	100 %

JR = Junior Researchers, MCR = Mid-Career Researchers, ANC = antenatal care

Discussion

In the past, research support was often a straightforward activity, as it relied on the donation of money by wealthy individuals to trusted people. A classic example was the development of the "harmonic telegraph" by Graham Bell under funding from his wealthy father-in-law (Bellis, 2023).

In developing countries, research grants have often focused on specific topics or issues, such as infectious and communicable diseases (Pukrittayakamee, 2004). Most grants were from rich countries, and awarded to Western academics. Over recent decades, there is a growing support for building the research capacity of low-and middle-income countries. This extends to the direct funding of local investigators living in these countries (Pukrittayakamee et al, 2018; Chotivanich & Pukrittayakamee, 2014).

To address this situation, the ADB has supported the creation of a Competitive Research Fund, which has supported 44 research projects carried out by the early and mid-career staff of UHS, Lao PDR. The setup of this CRF included also a capacity-building package via workshops, and mentoring by senior researchers. The CRF implementation has been a complex endeavor, as it required the management of 44 different research contracts (with individual Pas), which needed to be aligned with the requirements from both ADB and the UHS. As such, it required a joint collaborative effort from the organizing team and resources experts. As shown in this analysis, the CRF theme has proven to be successful in terms of the disbursement of grants by donors and is an effective conduit of research funds to grant recipients.

In consistent with UHS priorities, CRF research projects prioritized young and mid-career researchers, the research projects were fairly well distributed across a broad range of UHS faculties, signifying non-bias of grant distribution. The majority of projects (91%) focus on risk or service assessments, addressing health hazards and health services. Over one-third of the projects addressed communicable diseases (38.6%) and/or maternal and child health issues (36.3%), and projects prioritized the identification of solutions, to improve service delivery. Given their practical focus, these projects will help better under health hazards, and identify the solutions to healthcare delivery challenges in Lao PDR.

This analysis of the CRF awards suggests that, when coupled with coaching and workshops, competitive research funds can be an efficient way to build research capacity in low- and middle-income countries. To this end, countries can depend on South-South collaboration, both from academics from neighboring countries (i.e. Thailand) and Western academics residing in-situ (in this case, Lao PDR). The collaboration amongst institutions is also key since, as reflected in this case, which involved managing 44 different research contracts, the administrative and financial requirements can be complex. By addressing these challenges, developing countries can significantly improve their research capacity, and improve their health services over the long run.

About the Authors

Sasithon Pukrittayakamee is a Fellow of the Royal Society of Thailand and an Emeritus Professor of Faculty of Tropical Medicine, Mahidol University. Her clinical research background is tropical diseases focusing on malaria, influenza, Covid-19, and control of malaria in Thailand and neighboring countries. She is working in collaboration with the Mahidol-Oxford Research Unit, University of Oxford.

Mayfong Mayxay is a Professor and Vice-President at University of Health Sciences (UHS), Vientiane, Lao PDR and also a Visiting Professor of Tropical Medicine at University of Oxford, UK. He is also the Chairman of Research Promotion and Development of UHS. His research interests include varieties of infectious diseases, AMR, and public health particularly mother and child health.

Elizabeth Ashley is Director of the Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit and a Professor of Tropical Medicine at the University of Oxford UK. She is a physician trained in Infectious Diseases and Microbiology. Her research interests include malaria, diagnosis and treatment of infectious diseases, and antimicrobial resistance.

Kesinee Chotivanich is an Associate Follow of the Royal Society of Thailand and a Professor of Tropical Medicine, Mahidol University. She is the head of laboratory malaria in Mahidol-Oxford University Research Unit. Her interests are malaria pathophysiology and pharmacodynamics of antimalarial drugs. She provides clinical-related laboratory training and works with malaria research teams on international multi-center clinical trials, especially for tracking artemisinin resistance.

Sysavanh Phommachanh graduated in medicine, and obtained Master's degree in Health Social Sciences at Mahidol University, Thailand, research fellowship in Japan, a Ph.D. in Public Health at VU Amsterdam University, Netherland. A lecturer and researcher, currently position is the Vice-Director of IRED and in charge of health education and research development. She also is a Vice-President of the Research Ethic Committee of the UHS, a Steering Committee of the LaoHUN, and editing-editor of Lao Medical Journal.

Alexo Esperato is a Senior Health Specialist at the Asian Development Bank (ADB). In this role, he implements projects to strengthen the health systems of Southeast Asian countries. Before joining ADB in 2022, he worked on health systems strengthening in Latin America, the Middle East, and India.

Authors' Note

The views expressed in this article are those of the authors and do not necessarily reflect the views and policies of the Asian Development Bank or its Board of Governors, or of the governments they represent

TA-9397-REG is supported by the Asian Development Bank, 2018. Regional: Supporting Education and Health Sector Programs Facility. This information is accessible to ADB management and staff. It may be shared outside ADB with appropriate permission.

Acknowledgements

We would like to thank the Asian Development Bank for its support to this initiative through TA9397-REG. We are grateful to the CRF committee members including Anthony Black, Somphou Sayasone, Pimpha Paboriboun and Kongkham Sisouk for reviewing the CRF projects. Many thanks to Maricelle C.David (Associate Project Analyst), Connie Delos Santos (CRF's Financial Coordinator) and Phouthalaty Sihapanya (Project Assistant) for their excellent coordination.

References

Bellis M. Biography of Alexander Graham Bell, Inventor of the Telephone. ThoughtCo, 2022 May 26 [cited 2023 Aug 23] https://www.thoughtco.com/biography-alexander-graham-bell-4066244.

Asian Development Bank. Who we are. 2023 August 31 [cited 2023 August 31] https://www.adb.org/who-we-are/main.

Asian Development Bank. Regional: Supporting Education and Health Sector Programs Facility. 2017 Oct [cited 2023 August 31] https://www.adb.org/projects/47136-005/main.

Pukrittayakamee S. The evolution of clinical research [in Thai]. The Journal of the Royal Institute of Thailand 2004; 29: 898-911.

Pukrittayakamee S, Poovorawan K, Peto TJ, Phumratanaprapin W. Reflections on historical pandemics and Mahidol University's research on the treatment and prevention of Influenza outbreaks. The International Journal of the Royal Society of Thailand 2018: X; 1-14.

Kesinee Chotivanich and Sasithon Pukrittayakamee. Treatment and Prophylaxis of Influenza Infection: A Review of Relevant Research at Mahidol University. The Journal of the Royal Institute of Thailand 2014; 6: 82-86.

Sustaining Health Research During the COVID-19 Pandemic: Lessons from Field Sites in Rural Cambodia

Dysoley Lek[1,2*], Bipin Adhikari[3,4*], James J Callery[3,4*], Rupam Tripura[3,4*], Mom Ean[1], Moul Vanna[5], Nicky Almasy[6], Bunreth Voeurng[7], Phaikyeong Cheah[3,4], Kesinee Chotivanich[8], Thomas J Peto[3,4]

Abstract

Globally, the COVID-19 pandemic caused unprecedented difficulties to medical research collaborations during 2020-22. Mahidol-Oxford Tropical Medicine Research Unit (MORU) has field research sites in Cambodia which braced various challenges due to pandemic. We discuss how MORU's field research sites responded to the challenges brought by COVID-19 pandemic. During the pandemic, field research continued a chemoprophylaxis trial in northeast Cambodia that recruited 1400 patients; western Cambodia established operational research that involved 120 village malaria workers (VMWs) and recruited >4500 patients across two provinces, a multi-site clinical trial recruited 220 vivax patients, and another operational study recruited 1344 febrile and vivax patients in the communities through 27 VMWs. In addition, engagement activities involved youth groups (n = 25) from a local school including authorities from various levels as and when required. All of these studies and activities operated through the

[1] School of Public Health, National Institute of Public Health, Phnom Penh, Cambodia
[2] National Centre for Parasitology, Entomology and Malaria Control, Phnom Penh, Cambodia
[3] Mahidol Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
[4] Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK
[5] Action for Health and Development, Battambang, Cambodia
[6] NA Productions, Kuala Lumpur, Malaysia
[7] Provincial Health Department, Battambang, Cambodia
[8] Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
* Joint first authors
Correspondence to
Dysoley Lek (MD). Email: soleycnm@gmail.com
Dr Thomas J Peto (PhD). Email: tom@tropmedres.ac

pandemic. To ensure these studies were uninterrupted, after initial discussions among all partners efforts were made to continue research with precautionary adaptations to activities determined by the pandemic situation as it evolved over time. Community-based studies were implemented without mass gatherings and so engagement strategies were adapted to avoid the risk to participants of high-risk exposure events. Clinical trials continued to recruit patients where personal protective gear was available. High COVID-19 vaccination coverage in Cambodia also offered early relaxations of government-imposed restrictions which allowed to continue the ongoing research. During travel restrictions novel monitoring and supervision strategies were necessary and remote monitoring and teleconferencing was introduced. In some studies, serious delays to supplies were experienced and patient recruitment was curtailed but this occurred within acceptable limits. Building on the pre-established collaborations with the national and international partners, MORU's field sites adapted and utilized the flexible approaches to continue the ongoing studies. Although delays and difficulties due to COVID-19 restrictions affected some aspects of our research, strong collaboration, trust among the partners, and adaptations facilitated the successful completion of the studies.

Keywords: health research; collaboration; COVID-19 pandemic; multi-stakeholder engagement

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known case was identified in December 2019 in Wuhan, China and from there the outbreak then rapidly spread internationally (Sharma et al, 2020). The Emergency Committee of the World Health Organization declared a Public Health Emergency of International Concern (PHEIC) on the 30th of January 2020 (WHO, 2020). Thereafter, the pandemic itself, and the drastic measures taken in response to limit COVID-19 transmission, caused immediate and unprecedented difficulties to all counties in early 2020. The medical and public health systems and medical research have been severely impacted upon during 2020-22 (Moynihan et al, 2021). During the first years of the pandemic, implementing research in Southeast Asia was affected by border closures and travel restrictions, the redirection

of resources and redeployment of staff, and the need for hygienic precautions during contact with patients and study participants (Downey et al, 2022). Research focused on the control of multidrug-resistant falciparum malaria and its elimination in the Great Mekong Subregion is a competing health priority and could not be stalled despite the international situation due to COVID-19. In this article, we discuss the lessons learnt while conducting field research in remote sites in Cambodia during the COVID-19 pandemic.

History of collaboration between Mahidol, Oxford, and CNM

The Mahidol-Oxford Tropical Medicine Research Unit (MORU) was founded in 1979 and is a partnership between Thailand's Mahidol University, based at the Faculty for Tropical Medicine, Bangkok, and the University of Oxford, UK. It is funded by the UK's Wellcome Trust. The MORU Tropical Health Network includes 5 research units and approximately 50 collaborative clinical research sites. Mahidol's Faculty of Tropical Medicine, and Oxford's Centre for Tropical Medicine and Global Health are both internationally recognised centres of excellence for medical research into infectious diseases of poverty. In Cambodia, MORU has collaborated for decades with the Ministry of Health's National Centre for Parasitology, Entomology and Malaria Control (CNM) to conduct studies on malaria and other important infectious diseases. CNM has many roles, among which is the management of a national village malaria worker program to provide early diagnosis and treatment to rural populations.

Malaria transmission in Greater Mekong has declined significantly since the millennium but progress towards elimination is under threat from the emergence and spread of multidrug-resistant falciparum parasites (van der Pluijm et al, 2019). Hence, studies to improve treatments and identify elimination strategies are of urgency to the Cambodia and internationally (von Seidlein et al, 2019).

The Cambodian village malaria worker expansion study

Launched on 2013, the Global Fund's Regional Artemisinin-resistance Initiative (RAI) was established as a coordinated response to the emergence of drug-resistant malaria in the Greater Mekong subregion. The RAI is the major funder of malaria control and elimination in the region and in the 3rd round of funding a grant was received in late 2020 to implement operational research in Cambodia. This project was conducted by CNM, MORU and an experienced local NGO Action for Health and Development (AHEAD). The CAM-VMW study (ClinicalTrials.gov Identifier: NCT05045547) aimed to expand the role of VMWs to cover more than just malaria and

thus encourage participants with febrile illness to continue to attend village malaria workers. Patients were tested by novel rapid diagnostic tests (dengue and C-reactive protein rapid tests [RDTs]) in addition to their standard malaria tests. VMWs were trained to conduct a package of activities 1. disease surveillance; 2. management of mild common illnesses 3. hygiene and sanitation & 4. Expanded Program on Immunization (EPI) and antenatal care (ANC); that they carried out alongside their traditional job of treating malaria. In the same villages we conducted a project for the South and the Southeast Asia Community-based Trials Network entitled *"Incidences, Causes, and Outcomes of Febrile Illness in Rural South and Southeast Asia"* (SEACTN-WP-A) (ClinicalTrials.gov Identifier: NCT04478578) with support from the Wellcome Trust, UK (Chandna et al, 2021).

The Battambang and Pailin provinces study sites

New field sites were established in Pailin and Battambang provinces in western Cambodia to conduct this work in approximately 82 villages and 9 health centres and involving the training of approximately 120 village malaria workers (Figure 1).

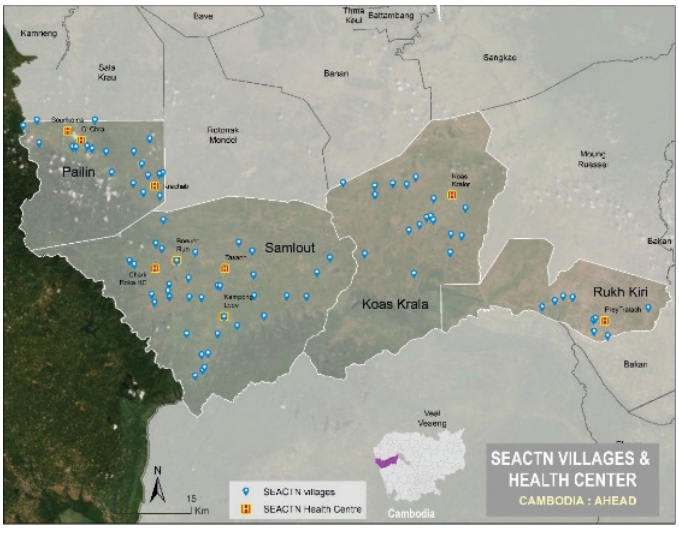


Figure 1 A map of the villages and health centres participating in a Global Fund supported project in western Cambodia. The large study area requires supervision and during COVID-19 lockdowns novel approaches to monitoring work were adopted.

Implementation of research was challenging here because the research partnership between AHEAD and MORU was newly created and the teams had not met in person before the COVID-19 pandemic began and travel became impossible, and the first physical meeting between staff was not until spring 2022. Therefore, training was done remotely using teleconferencing and additional activities were set up for monitoring data remotely and to support the local partner to meet research requirements. Implementation of training and community sensitization had to be conducted without assembling large groups at any one time to limit the risk of COVID-19 transmission. Delays in supplies also delayed the initiation of study activities, as did the fact that key members of the MORU team were redeployed away from malaria to work on COVID-19 itself during 2020-22. In the field, staff, volunteers and participants were trained on hygiene and supplied with protective materials as available, chiefly by the supply of face masks and gloves.



Figure 2 A village malaria worker performs a novel malaria and C-reactive Protein rapid diagnostic test as part of operational research to expand the role of community health workers.

One positive aspect from the pandemic was the increased interest in disease epidemiology by the village malaria workers who requested training on COVID-19 as part of their education on disease surveillance and they proved themselves keen to disseminate their new knowledge to their peers in the villages where they lived.

The Siem Pang health centre field station

Facilities at the health centre in Siem Pang, Stung Treng province, northeast Cambodia, were established in 2018 beginning with the renovation of the study ward, an office, and the establishment of a laboratory. The site has since been used to conduct community-based trials, malaria treatment studies of both Plasmodium vivax and plasmodium falciparum, and extensive community engagement and health education activities (Tripura et al, 2022; Peto et al, 2022; Ean et al, 2021; Callery et al, 2021; Sanann et al, 2019).

Research activities continued with only limited periodic interruptions despite inter-provincial travel being curtailed at many times. Many local communities are composed of ethnic minority groups living in forests and along local rivers. During the pandemic, fears of outsiders bringing in infections meant that many villages cut themselves off from contact with the outside world and visitors were not permitted to enter. However, the trust built up during previous engagement activities and the strong local leadership of an experienced health care worker with an extensive community health background, meant that fieldwork could be carefully revised so as to overcome these concerns and patients continued to attend studies at health facilities, and the research team was welcomed when visiting for community-based research activities. Globally, building relationship and trust with the community members have been implicated as one of the critical foundations for ongoing and future research (Adhikari & Cheah, 2021a; Adhikari et al, 2021b; Adhikari et al, 2022).

The Siem Pang research site has successfully completed PAL trial and has been hosting three major studies. Among these three, two are multi-country clinical trials and the other is a youth engagement project. Among the clinical trials, first one is termed as Effectiveness of novel approaches to radical cure with tafenoquine and primaquine – a randomized controlled trial in *P. vivax* patients' (EFFORT) and the second one is a multi-centre randomised controlled non-inferiority trial to compare the efficacy, safety and tolerability of Triple Artemisinin-based Combination Therapies versus first-line ACTs + placebo for the treatment of uncomplicated *Plasmodium falciparum* malaria in Asia. Also known as DeTACT study. While EFFORT study has completed the sample size (n = 220) and is continuing to follow-up, DeTACT is ongoing with optimal recruitment rates.

Both studies ran without interruptions during COVID-19 pandemic because adaptations were made to align with the COVID-19 restrictions in addition to dedication of field staff. For instance, remote based monitoring and follow-up were encouraged through digital resources (tele-connections/communications) while field

staff were stand-by throughout the period. While the referral, recruitment and follow-up were smooth due to such adaptations, engagement project by virtue of its characteristics was unique and demanded interactions, and gatherings, for training and skills development. The engagement project entailed selecting and training young students from a school located at Siem Pang detailed below.

Youth Advisory Group on Health Research (YAGHR) engagement

Engagement project began by selecting and training young students from the local school at Siem Pang who were established as a youth advisory group on health research (YAGHR). YAGHR members were trained and supported by engagement team of MORU based on the schedule and plans aligning with the objectives of the YAGHRE. Training schedules, topics and activities were based on the recommendations by YAGHR members followed by discussion. During the peak of COVID-19, offering health education related to COVID-19 was considered appropriate. Local authorities also asked for YAGHR members' initiatives (health promotion related activities). Responding to the pandemic, and the call for health education in the communities, YAGHR members were trained on COVID-19 and preventive measures. YAGHR members also designed and prepared health education related to the pandemic and presented in their school and at vaccination centres. YAGHR members thus promoted COVID-19 related knowledge (in the school and at the community), including at the vaccination centres.

After the decline of pandemic and coinciding with the vaccination coverage, students further revised the list of health priorities which subsequently informed the topics to be discussed and trained at the MORU office. All disease were trained one by one in a co-learning environment where students were engaged in designing health education/promotional materials. In doing so, YAGHR members learnt a multitude of new skills such as using Microsoft Word, Excel, Power Point, and audio-visual software. YAGHR members also learnt how to use cameras, audio-visual instruments such as drone cameras and preparing videos, the later were also widely shared in social media. Range of YAGHR activities underpinning the objectives and goals are briefly documented in a YouTube video (MORU, 2022).

The malaria prophylaxis with artemether-lumefantrine trial

Forests in Southeast Asia can be foci of transmission of malaria, and people working in forests are exposed to mosquitoes and are at higher risk of infection (Sanann et al, 2019; Nofal et al, 2019; Parker et al, 2017). To address this challenge, the Global Fund supported a study of chemoprophylaxis among forest workers, which was trialled

during the height of the first wave of the pandemic (spring 2020 to January 2021), and the intervention proved to be highly efficacious (Tripura et al, 2023; Maude et al, 2021). This study to assess efficacy of artemether-lumefantrine prophylaxis against forest malaria in Cambodia (ClinicalTrials.gov Identifier: NCT04041973) was completed on time despite initial concerns that it would need to be postponed or abandoned due to COVID-19. In total, 1400 participants joined the study and treatment adherence and re-enrolment rates were considerably higher than anticipated despite the challenges.

The Cham Bok health centre field station

In the context of declining malaria transmission in Cambodia due to successful control measures, to increase recruitment into the EFFORT and DeTACT trials, during 2021 a new research station was established at Cham Bok in western Cambodia, close to forested areas and national parks in which malaria transmission persists. Beginning work in a new province involved developing new relationships with local partners and high-level support from CNM to explain the need to continue research while other activities were being closed due to the pandemic.

The development of triple artemisinin combination therapy trial

Resistance to artemisinins and partner drugs used in artemisinin combination therapies is a risk to malaria control and elimination in Southeast Asia. In Cambodia and elsewhere, MORU and partners have trialled triple artemisinin combination therapies to address this (van der Pluijm et al, 2019; Peto et al, 2022; van der Pluijm et al, 2020). A trial to compare the efficacy, safety and tolerability of combinations of 3 anti-malarial drugs against combinations of 2 anti-malarial drugs (ClinicalTrials.gov Identifier: NCT03939104) was scheduled to begin in 2020 but its start was delayed until 2021 due to constraints on training and logistics at the remote study sites in Pursat and Stung Treng. The ongoing study was able to take measures to catch up due to intensive efforts and support from partners, and it is now on course to achieve close to the initial target sample size of participants.

Kravanh research site in Pursat Province during COVID-19

Kravanh district is located within the Pursat province that consists of villages nestling along the periphery of Kravnah mountain (part of the Cardamom mountain range) with some areas tht are densely forested. Recognized as one of the major endemic districts for malaria, Kravanh as a research site for MORU was established in 2018 that coincided with the decline in malaria in Pailin and Battambang. MORU's research office was built within the confines of the Kravanh referral hospital where CNM, PHD and district hospital authorities generously offered a space.

Because Kravanh research site is located within the district hospital, is not far from the provincial hospital, and is well connected by the road networks, it is the central site for field researchers and staff to organize and plan other research sites.

Currently Kravanh research site is hosting three major studies that includes EFFORT, DeTACT and Roll out Radical Cure (RORC) study, and two other studies are currently being planned and stationed that includes verbal autopsy study, and household survey.

Among the studies that are hosted by Kravanh research site, EFFORT has completed the total sample size of 220 (co-contributed by Siem Pang and Chambak) and is following up patients until February 2023. Another major clinical trial DeTACT is progressing well soon to achieve the required sample size. DeTACT is also currently recruiting patients at Siem Pang, Kravanh and Chambak.

RORC—an operational study amidst the COVID-19 pandemic

The other study hosted and successfully completed by Kravanh site is RORC (Roll Out of Radical Cure for vivax malaria). RORC was an operational study that explored the feasibility and practicalities of deploying the SD biosensor among village malaria workers (VMWs) (Adhikari et al, 2022b). The SD biosensor is a device to quantitate Glucose-6 Phosphate Dehydrogenase (G6PD) enzyme to prevent potential haemolysis by radical cure regimen consisting of 8-aminoquinoloes. The study started in May 2021 right at the middle of pandemic and was implemented throughout the pandemic period. Several adaptations were made to ensure RORC operated in the community. For instance, at the outset, the number of attendees were restricted (for physical distancing), training sessions were frequented so that it could host only a small number of VMWs instead of convening all together. Remote monitoring was encouraged by providing smart phone devices so that VMWs could record the snapshots of biosensor readings. All VMWs tested G6PD among participants in the village (Figure 3). As pandemic slowly began declining in addition to increasing vaccine coverage rates, VMWs were visited at the community sites to observe their performance and resolve the queries at real time.



Figure 3 A VMW performs G6PD test using biosensor in a village in Kravanh

Timelines and administrative challenges

Early in the pandemic, many Southeast Asian countries were added to watch lists as high-risk countries, and whilst Cambodia wasn't initially on these lists it was quickly added. Being part of the University of Oxford, MORU was, therefore, subject to many of the rules and regulations instituted in the UK and those imposed by Mahidol University, Thailand. As a result, scientific research in Cambodia was not only impacted by the COVID-19 situation in Cambodia, but also by that in Thailand, the U.K, and for one particular study, Australia.

Despite limited testing capacity, the first few COVID-19 cases in Cambodia were discovered by early March 2020, and although neighbouring countries, such as Thailand, began implementing travel restrictions there were no restrictions on travel into Cambodia initially. Despite being initially sceptical of the threat posed by COVID-19, as further cases were identified, the Cambodian government, ordered the closure of schools, restaurants, bars and casinos and limited entry visas for foreigners. For MORU researchers based in Bangkok, this proved problematic as they were required to frequently travel to Cambodia to oversee and coordinate ongoing research projects. Consequently, a large burden of responsibility fell on the sole remaining MORU researcher who was based in Cambodia when the COVID-19 pandemic began.

By the end of March 2020, the first direct impact of COVID-19 on research in Cambodia was felt when researchers collectively decided to stop all community meetings and pause recruitment into "the malaria prophylaxis with the artemether-lumefantrine trial" (the only active trial at that time), with only those already recruited continuing to be followed up. With limited information available on how COVID-19

was spread and on how best people could best protect themselves, staff were advised to reduce their work hours in the office, use hand gel and masks, and if they experienced cough or fever they were to self-isolate at home for 14 days. At the same time, MORU researchers based in Bangkok were advised to work from home, further fragmenting the oversight of the research in Cambodia. This was followed by The University of Oxford issuing guidance "to pause or postpone all non-essential research involving face-to-face interactions (unless arrangements can be made for it to be conducted remotely or online), unless it was related to COVID-19 or was clinical research vital for patient care or safety."

As approval processes for non-COVID-19 research ground to a halt in the UK following a tsunami of COVID-19 studies requiring ethics approval (research undertaken by MORU requires Ethics approval from The University of Oxford, UK [OxTREC]), a Vivax Malaria Project (EFFORT) that was to be undertaken in Cambodia by MORU and Menzies, Australia, switched to firstly apply for Australian-IRB approvals (granted May 2020), in an effort to avoid protracted delays to study approval.

With future studies and funding for the study sites expected to be delayed, support for the study staff in Kravanh, west Cambodia, who had only recently completed another MORU malaria research project, was required. This proved problematic given the limited funding available however researchers were successful in supporting the staff through this period.

Given the relatively low number of cases of COVID-19, the vital nature of the research and the trust built up during previous engagement activities, the team in Siam Pang were able to restart recruitment into the PAL trial from the end of April 2020. There were a number of adaptions to manage the risk of COVID-19, i.e. conducting recruitment at the health centre were infection control measures could be more easily implemented. However, due to border restrictions, the team faced delays receiving study supplies and were unable to ship study blood samples for processing in Bangkok.

By the end of July, cases of COVID-19 were increasing in Cambodia, however, with local authorities' permission the team were able to continue working in the community whilst adhering to strict COVID-19 prevention measures i.e. mask wearing. There did not appear to be any local transmission, only imported cases from Malaysia and Indonesia which were mainly confined to Phnom Penh. There was, however, further uncertainty with the sole Cambodian-based MORU researcher requiring a visa renewal. Given the restrictions on entry visas for foreigners there was a risk that no MORU researcher would remain in Cambodia, thankfully this was not the case.

Despite delays, approvals for new studies were granted (DeTACT study – June 2020, EFFORT study – August 2020 (UK) and October 2020 (Cambodia)) and the Kravanh study site was reactivated after many months of dormancy. This presented further logistic difficulties, as the MORU and Australian-based researchers were unable to visit due to travel restrictions resulting in, the already-stretched, sole MORU researcher having to relocate to Kravanh to set up the studies. MORU-based researchers did explore the possibility of obtaining Cambodian visas, however, despite malaria remaining a health priority, it ultimately proved too difficult and it wasn't until October 2021 that a 2nd MORU investigator was able to enter Cambodia.

By the end of 2020, it became apparent that COVID-19 transmission was occurring in Cambodia. This resulted in the Ministry of Health quarantining and testing over 9,000 high-risk contacts and Phnom Penh being considered a high-risk zone for Cambodia. Nevertheless, confirmed cases remained relatively low (< 350), with only 27 active cases but there were concerns that this increase in cases would impact the new projects.

In spite of the COVID-19 issues, the PAL trial reached the recruitment target by early December and completed all follow-ups by February 2021. The first batch of study samples were finally shipped to Bangkok in December, four months after the first contact with the courier service (due to COVID-19 restrictions).

Although the COVID-19 situation was worsening, research activities were able to continue and the 2021 Annual CNM Malaria Conference went ahead in March. Study training for the EFFORT study was delivered remotely via digital platforms by researchers based in Australia and the first patient was recruited in April 2021. However, with COVID-19 cases rising exponentially (Worldometer, 2023), it became apparent, that research would be impacted as the government imposed a two-week lockdown in Phnom Penh and the Prime minister warned that Cambodia was "on the brink of death" (Johnson 2022). Fortunately, the EFFORT study was able to continue, whilst adhering closely to the MoH COVID-19 guidelines, as they had an experienced team managing Plasmodium vivax-infected patients, and had built a good relationship with the local provincial health department. The DeTACT study similarly was able to complete training and begin recruitment by July due to the research on multidrug-resistant Plasmodium falciparum malaria being of great importance to Cambodia.

Unfortunately, another study, "Evaluating expanded roles for VMWs and exploring the main causes of febrile illness" (CAM-VMW), that was to run in Battambang/Pailin was delayed due to 1) delays in Cambodian Ethics approval being granted, 2) restrictions of movements within Cambodia, 3) logistic difficulties

supplying study materials from Bangkok and 4) setting up a new study site with a new study partner, a local NGO, AHEAD. Despite receiving approval in July 2021, the CAM-VMW was only able to officially launch in November 2021 due to delays in the manufacturing and supply of Dengue and Malaria/CRP RDTs from Korea. Since then all studies have continued to successfully recruit, and COVID-19 case numbers have plateaued.

Discussion

COVID-19 pandemic presented an unprecedented challenge to the health system globally, the brunt of the pandemic was experienced relatively prominently in resource limited settings (Mishra et al, 2022). Cambodia is one of the low- and middle-income countries (LMICs) within Greater Mekong Subregion that struggled with the resources to tackle the COVID-19 pandemic. Echoing with the global strategy, Cambodia implemented nationwide lockdown that entailed various restrictions on travelling, and thus inevitably restrictions on research related movements (e.g. human resources, logistics and supplies). The lockdown and restrictions posed major challenges in initiating new and continuing the ongoing research. Despite of these challenges, MORU together with CNM was able to maintain the research activities and thus bears essential lessons that can be useful for future research and implementations.

Firstly, MORU had an existing partnership with CNM since the first antimalarial research conducted in Pailin, western Cambodia in 2007. The 2007 antimalarial research revealed the first identification of Artemisinin Combination therapy (ACT) resistance, which was a major public health concern that informed the subsequent research in malaria not just in Cambodia but around Greater Mekong Sub-region and elsewhere. The implications of the research in western Cambodia soon became the hallmark for future of malaria research globally and also added to the need for and significance of MORU-CNM partnership. During the conduct of research in western Cambodia and subsequently around the malaria endemic districts within Cambodia, MORU's researchers and CNM partners strengthened the partnership through co-sharing of resources (for e.g. research ideas, administrative and regulatory support, policy translation and scientific output). Also, continuous presence of MORU in Cambodia, ongoing collaborations and interactive relationships with CNM built and institutionalized trust between researchers and the CNM counterparts. Trust and relationship building have been implicated as one of the major foundations for success of research, implementation and participation uptake (Adhikari et al, 2018; Adhikari et al, 2022a).

Engaging with the authorities at various levels (from central to the village level), having a collaborative relationships with various partners have been identified as essential elements of effective community engagement (Adhikari et al, 2017; Lavery et al, 2010) and has been one of the major drivers of success behind research conducted in Cambodia by MORU (Peto et al, 2018a; Peto et al, 2018b). Secondly, while retaining authority support and collaboration through pre-established relationships are highly valuable, they are equally fragile and dependent on the health of the relationship, meaning how such relationships are groomed over the years is critical (Adhikari et al, 2019; Kaehler et al, 2019). MORU's partnership and relationship with CNM are thus continuously building, and dynamic and are also predicated on agenda for research and implementation (Adhikari et al, 2017; Peto et al, 2018a). New research, and context such as brought by pandemic therefore are likely to affect the collaboration, that's when flexibility becomes an important jewel to keep the relationships and collaboration 'living' for both sides (Adhikari et al, 2017; Vincent et al, 2022). MORU's researchers have been flexible with the collaborators including adapting and accommodating the suggestions by CNM and other partners such as funders, and the ground staff (Peto et al, 2018a; Peto et al, 2018b). Flexibility of MORU and the partners remains to be a major element for the success of research in Cambodia.

Thirdly, during the pandemic, despite desire to conduct the research as stated by the protocol, particularly as outlined in the plan (timeline), researchers adapted the research by coping through the delays, administrative hurdles, restrictions, and logistic disruptions. The flexibility to accommodate the pandemic and conduct research based on the feasibility was a major lesson that allowed the success of research in Cambodia (Adhikari et al, 2022b; Peto et al, 2018b). In regard to operationalities of research, specifically tailoring the research based on the evolution of social and cultural context (sometimes through formative research) has been implicated as one of the major elements of effective community engagement for research implementation (Adhikari et al, 2017). Also, during the pandemic, because of the restrictions, more and more digital resources were utilized, reducing the face-to-face interactions. For instance, size of the face-to-face meetings were reduced at the cost of increasing the frequency of meetings in roll out radical cure community-based research project (Adhikari et al, 2022b; Adhikari et al, 2023). While digitalization of health care is already a flourishing success in the west, inclination towards the use of digital resources in LMICs has become a new norm and perhaps more and more technologies will be adopted in health care in the future (Adhikari et al, 2023; Mitchell & Kan, 2019). MORU similarly, utilized meetings and coordination through digital technologies even in the remote villages as and when possible because of pandemic and is believed to have supported the continuation of ongoing research (Thriemer, 2023).

Conclusions

MORU and CNM had a pre-existing partnership that was already generating evidence on antimalarial resistance and thus had a global significance which enhanced the values of the partnership and over the years strengthened the relationship. The strong ties between CNM and MORU thus helped continue research activities even during the pandemic although there were delays and disruptions. Flexibility of MORU, CNM and partners through the pandemic and adaptations of research to cope with the pandemic were major factors that contributed to the success of research implementation during pandemic in Cambodia.

About the Authors

H. E. Prof. Dysoley Lek is Deputy Director of the Centre for Parasitology, Entomology and Malaria Control (CNM) in Cambodia. He coordinates several major international collaborations between CNM and research partners. He is professor at the National Institute for Public Health with responsibilities for teaching and research.

Bipin Adhikari is a research clinician in the Department of Malaria and Critical Illness at the Mahidol-Oxford Tropical Medicine Research Unit, with a focus on qualitative research and methods in tropical medicine. He has worked on a wide range of diseases of poverty and has extensive field experience. He has published widely on engagement and the roles of community health workers

James J Callery is a research physician in the Department of Malaria and Critical Illness at the Mahidol-Oxford Tropical Medicine Research Unit, specialized on clinical studies of malaria in Southeast Asia. He trains and supervises clinical research teams at study sites. He has a particular interest in the clinical pharmacology of antimalarial combination therapies, and has completed major work on COVID-19 prophylaxis.

Rupam Tripura is a clinical epidemiologist in the Department of Malaria and Critical Illness at the Mahidol-Oxford Tropical Medicine Research Unit, with extensive experience of the design and implementation of hospital-based and community-based epidemiological and clinical studies in Asia.

Mom Ean leads the Siem Pang research station for the Department of Malaria and Critical Illness at the Mahidol-Oxford Tropical Medicine Research Unit. She is a trained nurse with long experience of community medicine and public engagement. She has implemented successfully a major clinical trial of antimalarial prophylaxis among forest goers.

Moul Vanna is a medical doctor and the Executive Director of Action for Health and Development (AHEAD) an NGO that works to improve the health of poor an under-served communities in rural Cambodia. She collaborates with partner organizations to implement studies of health and coordinate research with local stakeholders.

Nicky Almasy is a professional photographer, video-maker, and published author with a special interest in health and culture in Asia. He has worked on community engagement and public engagement for clinical research to improve the communication with and representation of study participants and their communities.

Bunreth Voeurng is the Director of the Provincial Health Department in Battambang, Cambodia. He is an experienced physician and he the coordinates the implementation of health services and the accompanying medical research done to support health. He was responsible for the response to COVID-19 in Battambang and is currently pursuing a doctoral degree based on the data from this activity.

Phaikyeong Cheah is the Head of Bioethics and Engagement at the Mahidol-Oxford Tropical Medicine Research Unit. A highly-cited researcher, she has a particular interest in engagement with vulnerable study populations so that they are able to participate in medical research. A pharmacist by training, her current work covers a very wide range of diseases, studies and countries.

Kesinee Chotivanich is an associated Fellow of the Royal Society of Thailand and Professor of Faculty of Tropical Medicine, Mahidol University. She is the Head of the Malaria Laboratories and an international expert on antimalarial drug sensitivity, and has made major contributions to the control of drug-resistant falciparum malaria. She leads the coordination of research collaborations between FTM and its partner institutions.

Thomas J Peto is an epidemiologist in the Department of Malaria and Critical Illness at the Mahidol-Oxford Tropical Medicine Research Unit. His research is centred on malaria elimination in Southeast Asia and he conducts fieldwork in Cambodia. He previously worked in The Gambia on infant hepatitis B vaccination, and in Tanzania on severe malaria.

References

Adhikari B, Cheah PY. Vaccine hesitancy in the COVID-19 era. Lancet Infect Dis 2021a, 21: 1086.

Adhikari B, Pell C, Phommasone K, Soundala X, Kommarasy P, Pongvongsa T, Henriques G, Day NPJ, Mayxay M, Cheah PY. Elements of effective community engagement: lessons from a targeted malaria elimination study in Lao PDR (Laos). Glob Health Action 2017; 10: 1366136.

Adhikari B, Phommasone K, Kommarasy P, Soundala X, Souvanthong P, Pongvongsa T, Henriques G, Newton PN, White NJ, Day NPJ, et al. Why do people participate in mass anti-malarial administration? Findings from a qualitative study in Nong District, Savannakhet Province, Lao PDR (Laos). Malar J 2018; 17: 15.

Adhikari B, Pokharel S, Raut S, Adhikari J, Thapa S, Paudel K, G CN, Neupane S, Neupane SR, Yadav R, et al. Why do people purchase antibiotics over-the-counter? A qualitative study with patients, clinicians and dispensers in central, eastern and western Nepal. BMJ Glob Health 2021b, 6: e005829.

Adhikari B, Tripura R, Dysoley L, Callery JJ, Peto TJ, Heng C, Vanda T, Simvieng O, Cassidy-Seyoum S, Ley B, et al. Glucose 6 Phosphate Dehydrogenase (G6PD) quantitation using biosensors at the point of first contact: a mixed method study in Cambodia. Malar J 2022b; 21: 282.

Adhikari B, Tripura R, Peto TJ, Callery JJ, von Seidlein L, Dysoley L, Dondorp AM. Village malaria workers for the community-based management of vivax malaria. The Lancet Regional Health-Southeast Asia 2023; 9: 100128.

Adhikari B, Vincent R, Wong G, Duddy C, Richardson E, Lavery JV, Molyneux S: A realist review of community engagement with health research. Wellcome Open Res 2019; 4: 87.

Adhikari B, Yeong Cheah P, von Seidlein L. Trust is the common denominator for COVID-19 vaccine acceptance: A literature review. Vaccine X 2022a; 12: 100213.

Callery JJ, Sanann N, Tripura R, Buntau T, Peto TJ, Kunthea P, Pell C, Soviet U, Nguon C, Lek D, Cheah PY: Engaging ethnic minority communities through performance and arts: health education in Cambodian forest villages. Int Health 2021; 13: 188-135.

Chandna A, Shwe Nwe Htun N, Peto TJ, Liverani M, Brummaier T, Phommasone K, Ibna Zaman S, Sandar Zaw A, Batty E, Waithira N, et al. Defining the burden of febrile illness in rural South and Southeast Asia: an open letter to announce the

launch of the Rural Febrile Illness project. Wellcome Open Res 2021; 6: 64.

Downey LE, Gadsden T, Vilas VDR, Peiris D, Jan S. The impact of COVID-19 on essential health service provision for endemic infectious diseases in the South-East Asia region: A systematic review. The Lancet Regional Health-Southeast Asia 2022.

Ean M, Sanann N, Callery JJ, Pell C, Peto TJ, Tripura R, Cheah PY. Theory of change: Drama and arts-based community engagement for malaria research and elimination in Cambodia. Wellcome Open Res 2021; 6: 46.

Johnson S. Cambodia accused of using Covid to edge towards 'totalitarian dictatorship'. Available online at http://bit.ly/3XgJwo8 (Accessed on 8th January, 2023). 2022.

Kaehler N, Adhikari B, Cheah PY, von Seidlein L, Day NPJ, Paris DH, Tanner M, Pell C. Prospects and strategies for malaria elimination in the Greater Mekong Sub-region: a qualitative study. Malar J 2019; 18: 203.

Lavery JV, Tinadana PO, Scott TW, Harrington LC, Ramsey JM, Ytuarte-Nunez C, James AA. Towards a framework for community engagement in global health research. Trends Parasitol 2010; 26: 279-283.

Maude RJ, Tripura R, Ean M, Sokha M, Peto TJ, Callery JJ, Imwong M, Vongpromek R, Tarning J, Mukaka M, et al. Study protocol: an open-label individually randomised controlled trial to assess the efficacy of artemether-lumefantrine prophylaxis for malaria among forest goers in Cambodia. BMJ Open 2021; 11: e045900.

Mishra SR, Adhikari B. Covid-19 in Nepal and the Existential Predicaments of Poverty and Governance. In: The Covid-19 Crisis in South Asia. Routledge 2022; p73-87.

Mitchell M, Kan L. Digital Technology and the Future of Health Systems. Health Syst Reform 2019; 5: 113-120.

MORU. Embedding youth voices in health and health research in Cambodia. Available online at https://www.youtube.com/watch?v=5LtCHpLjyIQ&t=4s (Accessed on 7th December 2022). 2022.

Moynihan R, Sanders S, Michaleff ZA, Scott AM, Clark J, To EJ, Jones M, Kitchener E, Fox M, Johansson M. Impact of COVID-19 pandemic on utilisation of healthcare services: a systematic review. BMJ open 2021; 11: e045343.

Nofal SD, Peto TJ, Adhikari B, Tripura R, Callery J, Bui TM, von Seidlein L, Pell C. How can interventions that target forest-goers be tailored to accelerate malaria elimination in the Greater Mekong Subregion? A systematic review of the qualitative literature. Malar J 2019; 18: 32.

Parker DM, Tripura R, Peto TJ, Maude RJ, Nguon C, Chalk J, Sirithiranont P, Imwong M, von Seidlein L, White NJ, Dondorp AM. A multi-level spatial analysis of clinical malaria and subclinical Plasmodium infections in Pailin Province, Cambodia. Heliyon 2017; 3: e00447.

Peto TJ, Tripura R, Callery JJ, Lek D, Nghia HDT, Nguon C, Thuong NTH, van der Pluijm RW, Dung NTP, Sokha M, et al. Triple therapy with artemether-lumefantrine plus amodiaquine versus artemether-lumefantrine alone for artemisinin-resistant, uncomplicated falciparum malaria: an open-label, randomised, multicentre trial. Lancet Infect Dis 2022; 22: 867-878.

Peto TJ, Tripura R, Davoeung C, Nguon C, Nou S, Heng C, Kunthea P, Adhikari B, Lim R, James N, et al. Reflections on a community engagement strategy for mass antimalarial drug administration in Cambodia. Am J Trop Med Hyg 2018a; 98: 100-104.

Peto TJ, Tripura R, Sanann N, Adhikari B, Callery J, Droogleever M, Heng C, Cheah PY, Davoeung C, Nguon C, et al. The feasibility and acceptability of mass drug administration for malaria in Cambodia: a mixed-methods study. Trans R Soc Trop Med Hyg 2018b; 112: 264-271.

Sanann N, Peto TJ, Tripura R, Callery JJ, Nguon C, Bui TM, Nofal SD, von Seidlein L, Lek D, Dondorp AM, et al. Forest work and its implications for malaria elimination: a qualitative study. Malar J 2019; 18: 376.

Sharma A, Tiwari S, Deb MK, Marty JL. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): a global pandemic and treatment strategies. International journal of antimicrobial agents 2020; 56: 106054.

Thriemer K. Adapting international clinical trials during COVID-19 and beyond. Journal of the Society for Clinical Trials 2023; 20: 237-241.

Tripura R, von Seidlein L, Sovannaroth S, Peto TJ, Callery JJ, Sokha M, Ean M, Heng C, Conradis-Jansen F, Madmanee W, et al. Antimalarial chemoprophylaxis for forest goers in southeast Asia: an open-label, individually randomised controlled trial. Lancet Infect Dis 20223; 23: 81-90.

van der Pluijm RW, Imwong M, Chau NH, Hoa NT, Thuy-Nhien NT, Thanh NV, Jittamala P, Hanboonkunupakarn B, Chutasmit K, Saelow C, et al. Determinants of dihydroartemisinin-piperaquine treatment failure in Plasmodium falciparum malaria in Cambodia, Thailand, and Vietnam: a prospective clinical, pharmacological, and genetic study. Lancet Infect Dis 2019; 19: 952-961.

van der Pluijm RW, Tripura R, Hoglund RM, Pyae Phyo A, Lek D, Ul Islam A, Anvikar AR, Satpathi P, Satpathi S, Behera PK, et al. Triple artemisinin-based combination therapies versus artemisinin-based combination therapies for uncomplicated Plasmodium falciparum malaria: a multicentre, open-label, randomised clinical trial. Lancet 2020; 395: 1345-1360.

Vincent R, Adhikari B, Duddy C, Richardson E, Wong G, Lavery J, Molyneux S. "Working relationships" across difference - a realist review of community engagement with malaria research [version 1; peer review: awaiting peer review]. Wellcome Open Research 2022; 7: 13.

von Seidlein L, Peto TJ, Tripura R, Pell C, Yeung S, Kindermans JM, Dondorp A, Maude R. Novel approaches to control malaria in forested areas of Southeast Asia. Trends Parasitol 2019; 35: 388-398.

WHO. COVID 19 Public Health Emergency of International Concern (PHEIC). Global research and innovation forum: towards a research roadmap. 2020.

Worldometer. Cambodia coronavirus cases. Available online at https://www.worldometers.info/coronavirus/country/cambodia/ (accessed on 8th January 2023). 2023.

The First Licensed Malaria Vaccines: From RTS,S to R21

Borimas Hanboonkunupakarn[1,2], Podjanee Jittamala[2,3], Kittiyod Poovorawan[1,2], Kesinee Chotivanich[1,2,4], Sasithon Pukrittayakamee[1,2,4], Watcharapong Piyaphanee[1], Lorenz von Seidlein[2,5]

Abstract

Currently two licensed malaria vaccines have been shown to be safe and effective. The development of the first vaccine, RTS,S required about 30 years. The second vaccine, R21, is a subunit malaria vaccine belonging to the same class as RTS,S but with small changes in its molecular structure to improve the immunogenicity. Data from a field trial in Burkina Faso showed that R21 with the adjuvant Matrix-M (MM) is at least as safe and protective as RTS,S with the adjuvant AS01. The production capacity of RTS,S/AS01 is limited to 10 million doses annually. Considering the 3.3 billion people globally at risk for malaria and the requirement for 4 doses to achieve lasting protection, RTS,S/AS01 is unlikely to contribute to malaria elimination efforts globally. In contrast, the Serum Institute of India is currently scaling up the production of R21/MM and has the capacity to produce 100s of millions of doses R21/ MM annually. There is realistic hope that R21/MM will play a key role in global malaria eradication efforts in the coming years.

Keywords: malaria; vaccines; R21 matrix M; RTS,S; AS01 adjuvant; circum-sporozoite protein; GSK; Serum Institute of India; Bill and Melinda Gates Foundation; WHO

[1] Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.
[2] Mahidol-Oxford Tropical Medicine Research Unit, Bangkok, Thailand
[3] Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.
[4] Royal Society of Thailand.
[5] Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK
Correspondence to Lorenz von Seidlein (MD, PhD), Mahidol-Oxford Tropical Medicine Research Unit (MORU), Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand.
Email: lorenz@tropmedres.ac

Introduction

Compared to the rapid development of COVID-19 vaccines, the development of malaria vaccines has been a disappointingly sluggish and ultimately neglected field. COVID-19 vaccines were registered within a year of the discovery of the pathogen and a year later hundreds of millions of vaccine doses had been rolled out (WHO, 2023; Mathieu et al, 2023; New York Times, 2023). Malaria has been a constant threat for approximately 3.3 billion people globally and has already killed many more people than COVID-19 ever will, but it took more than 100 years from the discovery of the parasite for the first vaccine to be registered. Aside from the complicated malaria parasite organism and immunity, the generally impoverished characteristics of the population at risk for malaria may explain the low priority and delayed development of a malaria vaccine.

Rational, evidence-based malaria vaccine development started approximately 60 years ago with Ian McGregor and co-workers demonstrating in The Gambia that the passive acquisition of antibodies can protect against malaria (Cohen et al, 1961). Since then, a long list of malaria vaccine candidates has perished in various stages of development. The first serious malaria vaccine candidate, RTS,S was conceived by investigators at the Walter Reed Army Institute of Research (WRAIR) and was developed in a collaborative effort between WRAIR and the pharmaceutical company GlaxoSmithKline (GSK) (Gordon et al, 1995). RTS,S was found to be safe and afforded statistically significant protection compared to earlier malaria vaccine candidates. Yet the collaboration between WRAIR and GSK was not a partnership between equals. WRAIR brought intellectual property and GSK brought capital and production facilities into the collaboration. As so often when dealing with the pharmaceutical industry, the return on investment in the shortest possible time plays an all-encompassing role while public health priorities play at best a minor role. Malaria endemic populations are not a promising market for high returns irrespective of potential donor investments. Consequently, the clinical development of RTS,S made limited progress until the American billionaire Bill Gates was persuaded by advisors that RTS,S held great promise. From Gate's perspective a vaccine was the ideal tool to eradicate malaria, a technological solution for a complex problem (Gates W, 2011). The Bill and Melinda Gates Foundation (BMGF) invested upwards of a billion US dollars in the development of RTS,S in the first and second decade of the 21st century. This funding support came to a

sudden halt when the less than stellar results from the first large clinical trials in African children were announced (Agnandji et al, 2012). Bill was disappointed (Butler D, 2012). The former closest malaria advisors were replaced with Alan McGill who as a new head of the malaria programme had the unpleasant task to turn off the funding for RTS,S/AS01. Despite funding issues, RTS,S received a positive scientific opinion from a major, stringent regulator, the European Medicines Agency (EMA). While this assessment was encouraging, major donors including UNICEF require WHO prequalification to purchase products such as a malaria vaccine. But the relevant committees in the WHO were not convinced by several aspects in the dossier specifically the overall impact, safety, and cost effectiveness (WHO, 2015; WHO, 2016). To receive prequalification the WHO recommended a very large demonstration project (WHO, 2021). With the BMGF and GSK unwilling to fund such a study it took several years until this project finally took off in Ghana, Malawi, and Kenya, which confirmed that a four-dose schedule of RTS,S with the adjuvant AS01 was indeed safe and protective in young children. In July 2022 the WHO finally prequalified RTS,S/AS01, seven years after EMA had already concluded that RTS,S/AS01 was safe and protective (WHO, 2022). That is a seven-year delay in approval for a vaccine to prevent a disease which caused more than 600,000 deaths in 2021 alone (WHO, 2022).

An ideal malaria vaccine should be safe and well tolerated, provide life-long robust protection and be available at millions of doses to be rolled out annually at less than a dollar per dose. The less-than-ideal RTS,S vaccine is safe and well tolerated but confers less than complete protection for a limited duration. During the first days and weeks following RTS,S vaccination protection is over 90% (Neafsey et al, 2015). Over the following months protection rapidly wanes. In the pivotal trial that led to licensing, 15,460 children participated in 7 African countries with highly heterogeneous malaria epidemiology. Over 18 months of follow-up, a three dose regimen of RTS,S/AS01 conferred 46% protection against clinical malaria in 5 to 17 month old children, and 27% in 6 to 12 week old infants (RTSS_Clinical_Trials_Partnership, 2014). By the end of the trial during 38 to 48 months of follow-up vaccine efficacy decreased to 28% and 18% respectively (RTSS_Clinical_Trials_Partnership, 2015). In 2021, Chandramohan and Greenwood presented an alternative, more appropriate strategy to optimize the protection afforded by RTS,S/AS01 (Chandramohan et al, 2021). By combining a four-dose regimen of RTS,S/AS01 with seasonal malaria chemoprevention (SMC) administered just before the malaria season, the protective efficacy of the combination as compared with chemoprevention alone was 63% against clinical malaria, 71% against hospital admission with severe malaria, and 73% against death from malaria in trial sites in Mali and neighbouring Burkina Faso.

How does RTS,S work? The vaccine triggers an immune response against the circumsporozoite (CSP) protein, perhaps the dominant antigen of the sporozoite, which is the first stage in the life cycle of the *Plasmodium* parasite after the mosquito vector bites a human host (Regules et al, 2011). The sporozoite stays in the circulation only for minutes to hours before establishing an infection in the liver where the parasite matures into merozoites that are released in the bloodstream and are responsible for morbidity and mortality. The immune response triggered by RTS,S can therefore only protect against the initial stage in the life cycle of *P. falciparum* and does not protect against the blood stages of the parasite. RTS,S consists of virus like particles containing the C-terminus and central repeat regions of CSP (Regules et al, 2011). The C-terminus is fused to an HBsAg molecule of the Hepatitis B Virus (HBV) forming an RTS fusion protein (Figure 1). RTS is co-expressed in *Saccharomyces cerevisiae* with unmodified HBsAg which adds the second 'S' to RTS,S. When the yeast cells are lysed lipid protein particles form spontaneously with an RTS to S ratio of 1:4 (Figure 2). The critical CSP fusion protein makes up only 20% of the active vaccine component. An unintended but welcomed consequence of this mismatch is the excellent protection against HBV infection conferred by RTS,S/AS01 (Valea et al, 2020).

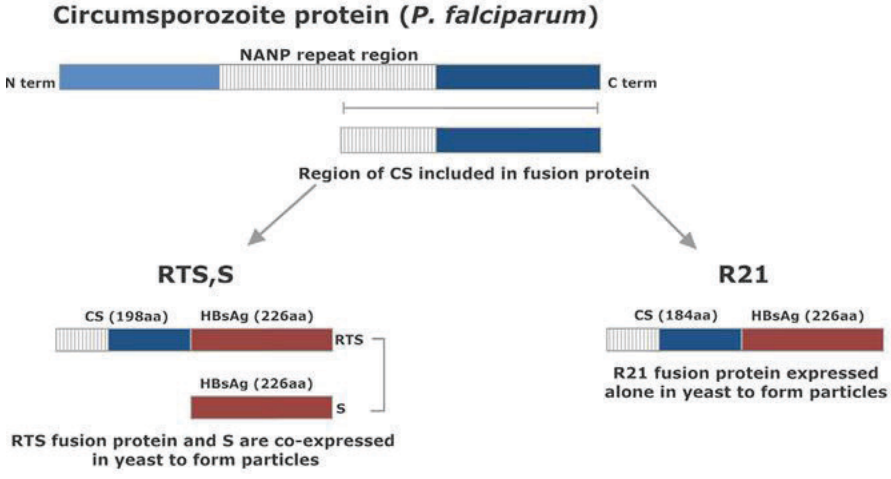


Figure 1 A schematic comparison of RTS,S and R21

Katie Collins and Adrian Hill working at the Jenner institute in Oxford recognized that this mismatch presents an opportunity to improve on RTS,S. They hypothesized that by increasing the CSP density on the surface of the protein the immune response could be increased. By switching from *S. cerevisiae* to *Pichia pastoris* as expression platform they were able to grow CSP at high density in the presence of an inducible alcohol oxidase AOX1 that ultimately resulted in the expression of an CSP-HBsAg fusion protein without HBsAg excess in R21 (Figures 1 & 2) (Collins et al, 2017).

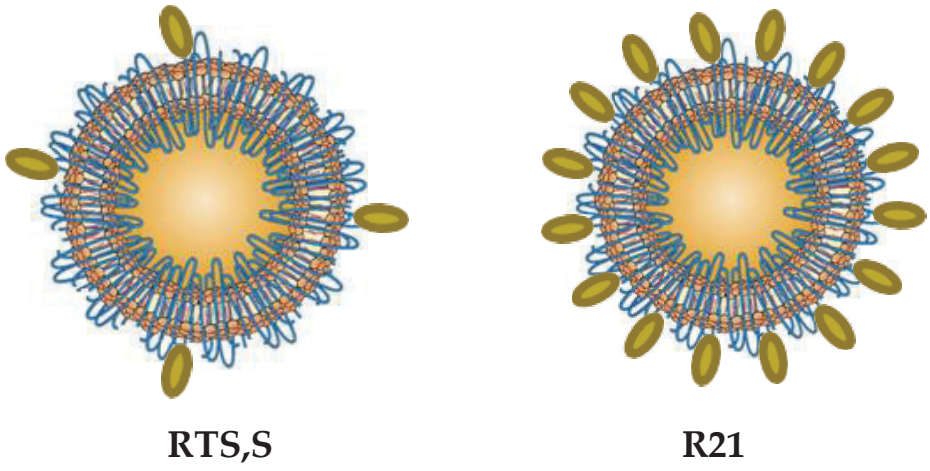


Figure 2 A schematic presentation of CSP linked to HBsAg in RTS,S and R21

What is the role of the adjuvant? Early studies of RTS,S demonstrated convincingly that the immune response depends on the adjuvant (Gordon et al, 1995). RTS,S is most immunogenic when administered with AS01 an adjuvant owned by GSK (Kester et al, 2009). This is a liposome-based adjuvant containing a saponin, QS-21, and monophosphoryl lipid A, a TLR4 agonist derived from bacterial lipopolysaccharide. The importance of the adjuvant led critics to speculate that the major commercial interest that motivated GSK to develop RTS,S was to collect data on AS01 which since has been critical for the registration of other GSK vaccines including the recombinant 'blockbuster' varicella-zoster vaccine Shingrix that helped GSK to beat fourth-quarter profit and sales forecasts in 2022 (Reuters, 2023). The GSK ownership of the intellectual property rights for AS01 makes it unlikely that competing malaria vaccine candidates can license AS01. Such pragmatic as well as scientific reasons suggested that Matrix M (MM) licensed from Novavax, composed of saponins, cholesterol, and phospholipids is the most appropriate adjuvant for R21.

Evidence that R21/MM is protective comes from a cohort of nearly 500 children aged 5 to 17 months enrolled in a randomised controlled trial in Nanoro, Burkina Faso. R21/MM had a favourable safety profile and was well tolerated. Most adverse events were mild and none of the seven serious adverse events were attributed to the vaccine. Following the administration of 3 doses of 5 μg R21 plus 50 μg MM, the protective efficacy was 77% (67 to 84) at 6 months (Datoo et al, 2021). Following a booster dose of 5 μg R21 plus 50 μg MM at Month 12 the protective efficacy was 80% (72 to 85) (Datoo et al, 2022). These efficacy estimates for R21/MM are better than the RTS,S/AS01 estimates from the large 7-country study (RTSS_Clinical_Trials_Partnership, 2014; 2015). There are several explanations. As mentioned earlier the malaria epidemiology in the 7 countries is highly heterogeneous and the vaccinations in RTS,S/AS01 trials were, in contrast to the R21/MM trials, not timed to immediately precede the malaria season. It should be obvious that for vaccines with rapidly waning protection like RTS,S/AS01 the estimate of protection changes rapidly over time. Another difference in the trial design is the coadministration of antimalarial drugs, which may influence estimates of protection. As many as 80% of the children participating in the R21/MM trial received antimalarial drugs as part of seasonal malaria chemoprevention routinely during the follow-up period. On the other hand, during the RTS,S/AS01 trial the investigators prevented the co- administration of antimalarial drugs for prevention or treatment of subclinical infections. Today it seems that the coadministration of antimalarial drugs with vaccinations has additive if not synergistic benefits (Chandramohan et al, 2021). As mentioned, vaccines targeting the sporozoite stage in the life cycle of *P. falciparum* does not impact circulating schizonts. Appropriate antimalarial drugs are needed to clear these blood stages of *P. falciparum*. Based onthe comparison of the R21/MM data from Nanoro, Burkina Faso and the data from combined SMC and seasonal vaccination trial in Burkina Faso and Mali by Chandramohan et al (2021). It seems that R21/MM is at least as protective and safe as RTS,S/AS01. The definitive answer on whether R21/MM is more protective than RTS,S/AS01 would require a randomised, controlled, double-blind trial comparing the two vaccines head-to-head, which is unlikely to be forthcoming.

While protective efficacy is critical when selecting a malaria vaccine, availability is just as relevant. GSK has made it clear that no more than 10 million doses RTS,S/AS01 will be produced annually, which covers only a fraction of the global demand. There is talk about a technology transfer to more economic vaccine producers some years in the future, but this means the vaccine implementation will be delayed and millions of people continue be exposed to potentially preventable risk. The WHO has developed a rationing plan prioritizing young African child, who are at highest

risk of dying from malaria (WHO, 2023). But not even for this high-risk group are the available vaccine doses sufficient. Elaborate rationing plans are currently being implemented (TDR, 2023). However, many people are not able and will not be able to get vaccinated with RTS,S/AS01 under these circumstances, including older children who with the changing epidemiology of malaria are increasingly at risk of dying from malaria, adults or people in very large malaria endemic regions outside of Africa.

If there is one positive lesson to be learned from the COVID-19 pandemic it may very well be the fact that if there is a will, billions of doses of novel vaccines can be rolled out within a year or two (Mathieu et al, 2021). Aware of the demand for malaria vaccines, the R21 development team at the Jenner Institute in Oxford is working with the Serum Institute of India Pvt. Ltd. on the scale up of R21/MM production. Serum Institute of India (SII) is the world's largest vaccine-producing company in the world's largest vaccine-producing nation, India (NPR, 2021). SII produces a range of childhood vaccines including measles, tetanus, pertussis, diphtheria, and hepatitis. SII also exports vaccines to 170 countries and estimates that two-thirds of the world's children are inoculated with its vaccines (NPR, 2021). During the COVID-19 pandemic investigators from the Jenner Institute worked closely with the SII on COVISHIELD, the ChAdOx1 nCoV- 19 recombinant corona virus vaccine. In December 2021 SII estimated that its monthly production capacity for COVISHIELD was approximately 250-275 million doses (The_Times_of_India, 2021). Considering the 3.3 billion people at risk globally for malaria, the need for a 4-dose vaccine regimen, and the need to include older age groups not only young children in malaria vaccination programmes, 100s of millions of vaccine doses will be needed annually. SII has the capacity and is willing to fill this demand.

In 2023 R21/MM received regulatory approval first in Ghana, then Nigeria, and most recently in Burkina Faso (Quartz, 2023, Guardian, 2023, University_of_Oxford, 2023). The WHO has recommended the use of R21/Matrix-M for malaria preventions in October 2023 and is likely that R21/MM will be prequalified later in 2023.

Author's Note

Funding: no funding was received for writing this article. Conflicts of interest: LvS is collaborating with the Jenner Institute and SII on the evaluation of the co-administration of R21/MM with antimalarial drugs.

About the Authors

Borimas Hanboonkunupakarn is a lecturer at the Department of Clinical Tropical Medicine, and a clinician at Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University. Her background is MD-PhD and DTM&H with experiences in Phase 1 and Phase 2 clinical trials. Her research interests are tropical disease, infectious disease and malaria focusing on safety and efficacy of triple artemisinin combinations and blocking of malaria transmission.

Podjanee Jittamala is Assistant Professor at the Department of Tropical Hygiene. She is a pediatrician with a specialization in infectious diseases. Dr. Podjanee's research expertise includes malaria epidemiology and conducting clinical trials to evaluate malaria treatment and elimination strategies in the region. She is also experienced in leading pragmatic trials, assessing the efficacy of treatments or therapies available for malaria in clinical practice conditions.

Kittiyod Poovorawan is an Associated Professor at the Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University. He is a medical doctor with expertise in internal medicine, gastroenterology, hepatology, and clinical research of tropical diseases. His primary research area is liver diseases included viral hepatitis, liver abscess, chronic liver diseases, and gastrointestinal involvement of tropical diseases.

Kesinee Chotivanich is an Associate Follow of the Royal Society of Thailand and a Professor of Tropical Medicine, Mahidol University. She is the head of laboratory malaria in Mahidol-Oxford University Research Unit. Her interests are malaria pathophysiology and pharmacodynamics of antimalarial drugs. She provides clinical-related laboratory training and works with malaria research teams on international multi-center clinical trials, especially for tracking artemisinin resistance.

Sasithon Pukrittayakamee is a Fellow of the Royal Society of Thailand and an Emeritus Professor of Faculty of Tropical Medicine, Mahidol University. Her clinical research background is tropical diseases focusing on malaria, influenza, Cocid-19, and control of malaria in Thailand and neighboring countries. She is working in collaboration with the Mahidol-Oxford Research Unit, University of Oxford.

Watcharapong Piyaphanee is an Associated Professor at the Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University. He is an internist and a specialist in Travel Medicine. Dr. Piyaphanee is the co-founder of the only Residency Training Program in Travel Medicine. His primary research area is in travel medicine field such as malaria/dengue infection among travelers, travelers' diarrhea, vaccine usages in travelers.

Lorenz von Seidlein has been working on global health for the last 25 years based in West Africa, South Korea, East Africa, Australia and most recently Thailand where he is employed by the Mahidol Oxford Research Unit. He is coordinating malaria elimination projects in Asia and working on a project in East Africa to provide better health through improved housing.

References

Agnandji ST, Lell B, Fernandes JF, Abossolo BP, Methogo BG, Kabwende AL, et al. A phase 3 trial of RTS,S/AS01 malaria vaccine in African infants. N Engl J Med 2012; 367: 2284- 2295.

Butler D. Malaria vaccine gives disappointing results. Nature 2012. https://doiorg/101038/nature201211785.

Chandramohan D, Zongo I, Sagara I, Cairns M, Yerbanga RS, Diarra M, et al. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. N Engl J Med 2021; 385: 1005-1017.

Cohen S, McGregor I, Carrington S. Gamma-globulin and acquired immunity to human malaria.

Nature 1961; 192: 733-737.

Collins KA, Snaith R, Cottingham MG, Gilbert SC, Hill AVS. Enhancing protective immunity to malaria with a highly immunogenic virus-like particle vaccine. Sci Rep 2017; 7: 46621.

Datoo MS, Natama HM, Some A, Bellamy D, Traore O, Rouamba T, et al. Efficacy and immunogenicity of R21/Matrix-M vaccine against clinical malaria after 2 years' follow- up in children in Burkina Faso: a phase 1/2b randomised controlled trial. Lancet Infect Dis 2022; 22: 1728-1736.

Datoo MS, Natama MH, Some A, Traore O, Rouamba T, Bellamy D, et al. Efficacy of a low- dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised controlled trial. Lancet 2021; 397: 1809-1818.

Gates W. Annual Letter. 2011. https://wwwgatesfoundationorg/ideas/annual-letters/annual-letter- 2011.

Gordon DM, McGovern TW, Krzych U, Cohen JC, Schneider I, LaChance R, Heppner DG, Yuan G, Hollingdale M, Slaoui M, et al. Safety, immunogenicity, and efficacy of a recombinantly produced Plasmodium falciparum circumsporozoite protein-hepatitis B surface antigen subunit vaccine. J Infect Dis 1995; 171: 1576-1585.

Guardian. Ghana is first country to approve Oxford malaria vaccine. 2023. https://wwwtheguardiancom/global-development/2023/apr/13/ghana-is-first-country-to-approve-oxford-r21-malaria-vaccine.

Kester KE, Cummings JF, Ofori-Anyinam O, Ockenhouse CF, Krzych U, Moris P, et al.

Randomized, double-blind, phase 2a trial of falciparum malaria vaccines RTS,S/AS01B and RTS,S/AS02A in malaria-naive adults: safety, efficacy, and immunologic associates of protection. J Infect Dis 2009; 200: 337-346.

Mathieu E, Ritchie H, Ortiz-Ospina E, Roser M, Hasell J, Appel C, Giattino C, Rodes-Guirao L. A global database of COVID-19 vaccinations. Nat Hum Behav 2021; 5: 947-953.

Mathieu E, Ritchie H, Rodés-Guirao L, Appel C, Giattino C, Hasell J, Macdonald B, Dattani S, Beltekian D, Ortiz-Ospina E, Roser M. Coronavirus Pandemic (COVID-19). https://ourworldindataorg/coronavirus. 2023.

Neafsey DE, Juraska M, Bedford T, Benkeser D, Valim C, Griggs A, et al. Genetic Diversity and Protective Efficacy of the RTS,S/AS01 Malaria Vaccine. N Engl J Med 2015; 373: 2025- 2037.

New York Times. Tracking Coronavirus Vaccinations Around the World. 2023. https://wwwnytimescom/interactive/2021/world/covid-vaccinations-trackerhtml.

NPR. The World's Largest Vaccine Maker Took A Multimillion Dollar Pandemic Gamble. 2021. https://wwwnprorg/sections/goatsandsoda/2021/03/18/978065736/indias-role-in-covid- 19-vaccine-production-is-getting-even-bigger.

Quartz. Nigeria follows Ghana in approving Oxford's R21 malaria vaccine. 2023. https://qzcom/nigeria-malaria-vaccine-r21-oxford-ghana-1850347118.

Regules JA, Cummings JF, Ockenhouse CF. The RTS,S vaccine candidate for malaria. Expert Rev Vaccines 2011; 10: 589-599.

Reuters. GSK beats expectations, shingles vaccine bolsters outlook. 2023. https://wwwreuterscom/business/healthcare-pharmaceuticals/gsk-reports-q4-profit-sales- beat-wall-street-estimates-2023-02-01/.

RTSS_Clinical_Trials_Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet 2015; 386: 31-45.

RTSS_Clinical_Trials_Partnership. Efficacy and safety of the RTS,S/AS01 malaria vaccine during 18 months after vaccination: a phase 3 randomized, controlled trial in children and young infants at 11 African sites. PLoS Med 2014; 11: e1001685.

TDR. Implementation strategies for delivering the RTS,S/AS01 malaria vaccine in countries with seasonal transmission. 2023. https://tdrwhoint/newsroom/news/item/25-04-2023- implementation-strategies-for-delivering-the-rts-s-as01-malaria-vaccine-in-countries- with-seasonal-transmission.

The_Times_of_India. Covishield production capacity 250-275 million doses a month. 2021. https://timesofindiaindiatimescom/india/covishield-production-capacity-250-275-million- doses-a-month-covaxin-50-60-million-govt/articleshow/88278989cms.

University_of_Oxford. Oxford R21/Matrix-M™ malaria vaccine receives regulatory clearance for use in Burkina Faso. 2023. https://wwwoxacuk/news/2023-07-24-oxford-r21matrix- m-malaria-vaccine-receives-regulatory-clearance-use-burkina-faso.

Valea I, Adjei S, Usuf E, Traore O, Ansong D, Tinto H, et al. Long-term immunogenicity and immune memory response to the hepatitis B antigen in the RTS,S/AS01(E) malaria vaccine in African children: a randomized trial. Hum Vaccin Immunother 2020; 16: 1464-1470.

WHO. Full Evidence Report on the RTS,S/AS01 Malaria Vaccine. 2021. https://cdnwhoint/media/docs/default-source/immunization/mvip/full-evidence-report-on- the-rtss-as01-malaria-vaccine-for-sage-mpag-(sept2021)pdf?sfvrsn=c9737be_5.

WHO. COVID-19 vaccine tracker and landscape. 2023. https://wwwwhoint/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.

WHO. Malaria vaccine: WHO position paper – January 2016. Weekly Epidemiological Record 2016; 91: 33-52.

WHO. Malaria vaccine: WHO position paper – March 2022. Weekly Epidemiological Record 2022; 97: 60-78.

WHO. Meeting of the Strategic Advisory Group of Experts on immunization, October 2015 – conclusions and recommendations. Weekly Epidemiological Record 2015; 50: 693-696.

WHO. RTS,S malaria vaccine. 2023. https://wwwwhoint/news-room/questions-and- answers/item/q-a-on-rts-s-malaria-vaccine.

WHO. World Malaria Report. 2022. https://wwwwhoint/publications/i/item/9789240064898.

Reflections on How to Diagnose and Classify Lymphoma

Sanya Sukpanichnant[1,2]

Abstract

Diagnosis and classification (D&C) of lymphoma have been improved in the past 120+ years since the first description and illustration of Reed-Sternberg cells in Hodgkin disease by Dorothy Reed in 1902. Morphologic approach paves the main path to the D&C of lymphoma. Then, immunologic approach unprecedentedly increases our understanding in lymphoid cells for better D&C of lymphoma since the introduction of the Lukes-Collins classification and the Kiel classification for non-Hodgkin lymphoma (NHL) in the early 1970s. Then, genetic approach comes in when Burkitt lymphoma was found to have a unique non-random karyotypic abnormality, the t(8;14) translocation, in 1982. Afterwards, more genetic information and the advances in molecular genetic studies help to segregate various clusters of lymphomas with morphologic resemblance. All these multiparameter approaches bring in better understanding and the better D & C of lymphomas but at the same times leaving pathologists and hematopathologists alike who cannot access to the sophisticated technics behind. While targeted therapies improves clinical outcomes since anti-CD20 immunotherapy in the past 25+ years, there is no guarantee about the benefit of the high-throughput workups over the conventional approach, using morphology and immunophenotype to the D&C of lymphoma with an appropriate rapid turnaround time under a good clinical correlation.

Keywords: reflection; diagnosis; classification; lymphoma; rapid turnaround time

[1] Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand
[2] The Academy of Science, the Royal Society of Thailand

Correspondence to Sanya Sukpanichnant (MD), Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. Email: sanya.suk@mahidol.ac.th

Introduction

This article of "reflections on how to diagnose and classify lymphoma" comes from the author's personal experience as a hematopathologist for 30 years since finishing training in 1993 at Department of Pathology, Vanderbilt University Medical Center with Professor Dr. Robert D Collins, one of the well-known hematopathologists in the early 1970s for the Lukes-Collins classification for lymphoma (Lukes & Collins, 1974). The author has been serving as a hematopathologist at Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University since June 1993. This government-based hospital is the largest hospital in Thailand. Every year, we diagnose approximately 250 new cases of lymphoma at this hospital and nearly 100 consultation cases from other hospitals and private laboratories. The authors has been involving in a good number of publications on lymphoma throughout the ongoing career (Swerdlow et al, 1993; Sukpanichnant et al, 1998; Sukpanichnant, 2004; Sukpanichnant et al, 2004; Pongpruttipan et al, 2012; Intragumtornchai et al, 2018; Sitthinamsuwan et al, 2018; Ngamdamrongkiat et al, 2022; Vangveeravong et al, 2022).

Reflections on how to diagnose and classify lymphoma

Since the first description and illustration of Reed-Sternberg cells in Hodgkin disease by Dorothy Reed in 1902 (Reed DM, 1902: 133-98), the diagnosis and classification (D&C) of lymphoma have been improved in the past 120+ years. Struggles, however, were encountered by morphology alone without understanding the nature of the lymphoma cells. At one time, lymphoma was defined as a malignancy of lymphatic tissue encompassing varieties of cells, not only lymphoid cells but also mononuclear phagocyte system cells and other supporting cells. Using comparison to the lymphocytes and reticulum cells given to any large mononuclear cells with close relationship to reticulin fibers as highlighted by histochemical stains, e.g., reticulum stain, NHL was once classified into 2 groups – lymphocyte (for the small cells) and reticulum cell (for the large cells) (Sundberg, 1947). Then, misunderstanding continued for nearly a decade when the large lymphoma cells were interpreted as histiocytes (Rappaport, 1966). It took a lot of research works and publications to demonstrate that the reticulum cell sarcoma or histiocytic lymphoma are in fact large lymphoma cells, either of B-cell or T-cell phenotype, in most cases of lymphoma with large cell morphology (Taylor & Hartsock, 2011; Jaffe, 2019).

Immunology provides us knowledge and better understanding in normal lymphoid cells and neoplastic ones. Nevertheless, it took time to accept immunologic approach to the D&C of lymphoma. Lukes-Collins classification (1974) and Kiel

classification (1975) initiated such an immunological approach (Lukes & Collins, 1974; Lennert et al, 1975). Unfortunately, in real world, simplicity won as the working formulation (WF) for clinical usage in classifications of NHL had been well accepted since its publication in 1982 (National Cancer Institute, 1982). In many countries, especially those with limited resources, morphological approach alone in this WF had been used for nearly 20 years until the well accepted 3rd edition of the WHO classification of tumours of haematopoietic and lymphoid tissues published in 2001 (Jaffe et al, 2001). But in developed countries, the updated Kiel classification (Stansfeld et al, 1988) had been used for nearly 20 years before the revised European-American Classification for Lymphoid neoplasms (REAL classification) published in 1994 (Harris et al, 1994). Then, the REAL classification transformed into the WHO classification, 3rd edition. Since then, the D&C of lymphoma requires 4 main findings – clinical, morphological, immunophenotypic, and genetic (Harris et al, 1994; Jaffe et al, 2001). Such a multiparameter approach has been carried out, mostly completely in the developed countries but not in the developing or underdeveloped countries where limited resources force the pathologic diagnosis of lymphoma based on morphology and a limited panel of immunohistochemistry (immunostaining).

Cytogenetic study has been introduced to search for a specific genetic marker in a particular type of lymphoma. Non-random karyotypic abnormality eventually paid off when the t(8;14) translocation was identified in 1982 in Burkitt lymphoma (Dalla-Favera et al, 1982; Taub et al, 1982). Later, molecular genetic technics allow us to detect rearrangements of immunoglobulin (Ig) genes and T-cell receptor (TCR) genes in B-cell and T-cell, respectively. Clonal rearrangement of Ig gene or TCR gene detected by polymerase chain reaction (PCR) in any tissue suspected of B-cell or T-cell lymphoma, respectively, supports the diagnosis of lymphoma as monoclonality considered as indicative of neoplasm (Jaffe, 2019).

Fluorescence in situ hybridization (FISH) provides detection of any genes of interest. In lymphoma, rearrangements of *BCL2*, *BCL6*, *MYC*, and *IRF4/MUM1* genes have been used to support the diagnosis of follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, high grade B-cell lymphoma (HGBCL) with *MYC* and *BCL2* rearrangments/HGBCL with *MYC* and *BCL6* rearrangements, and large B-cell lymphoma with *IRF4/MUM1* rearrangement (WHO Classification of Tumours Editorial Board, 2022), respectively. Then came gene expression profiling using array comparative genomic hybridization in order to compare patient's genome against a reference genome in term of gain or loss of chromosomes or subchromosomal regions. The first application of this molecular genetic technic was the determination of the cell

of origin in DLBCL – germinal center B-cell (GCB) or activated B-cell (ABC) – rendering subgrouping of DLBCL in term of different treatment regimens (WHO Classification of Tumours Editorial Board, 2022). Recently, genetic landscapes of many types of lymphoma have been published, giving the detailed genetic information about the typical cases of lymphomas in certain entities (WHO Classification of Tumours Editorial Board, 2022). Certainly, all of these genetic landscapes provide us better understanding in those entities of lymphomas, but the reflection on the molecular genetic advances is that how many cases of the so-called "typical" or "classic" entities of lymphomas are required – 20, 50, 100, or several hundreds – so that we can have confidence on the information provided by these perplexing genetic landscapes.

The last reflection to give is upon the essential diagnostic criteria given in each entity of lymphoma according to the beta version of the WHO classification of haematolymphoid tumours, 5th edition (WHO-HAEM5). The general introduction of the WHO-HAEM5 describes about essential and desirable diagnostic criteria for each entity as follow:

> "The essential and desirable diagnostic criteria for each entity are intended to facilitate distilling the key diagnostic components needed to classify a particular disease type. Essential diagnostic criteria are considered must-have features, whereas desirable diagnostic criteria are nice-to-have features (i.e. they support a diagnosis but are not mandatory). The listing of essential diagnostic criteria that have the broadest possible applicability is intended to aid in the applicability of the classification particularly in limited resource settings where feasible. It is hoped that the genetic underpinnings of the classification will prompt and urge the provision of local health resources to ensure that the necessary genetic testing platforms are available to peruse the full potential of the classification. The importance of such resources being available locally in some regions or even countries stems from the fact that sending out tests to remote reference labs tends to limit the availability of accurate public health data within the local community."
> (WHO Classification of Tumours Editorial Board, 2022)

But, in daily practice in countries with limited resource settings, some of the essential diagnostic criteria are still not accessible so that the making diagnosis of a specific lymphoma type may have problem. For example, in plasmablastic lymphoma (PBL), essential diagnostic criteria include 1) lymphoma with plasmablastic/immunoblastic morphology, 2) expression of plasma cell associated antigens (e.g.

MUM1, CD138, BLIMP1), and 3) negativity for CD20, PAX5, ALK and KSHV/HHV8 (WHO Classification of Tumours Editorial Board, 2022). If immunostaining for KSHV/HHV8 is not available then it cannot completely exclude KSHV/HHV8+ DLBCL before making a diagnosis of PBL. Importantly, the first essential diagnostic criterion for PBL needs to mark sure that it is lymphoma because it is well documented that plasmablast or immunoblast may be difficult to distinguish from large tumor cells in other non-hematologic malignancies such as carcinoma, melanoma, or sarcoma. Moreover, melanoma cells express MUM1 protein and both carcinoma and melanoma cells express CD138. [Kind et al, 2019; Natkunam et al, 2001] We recently published a case report of metastatic prostatic adenocarcinoma mimicking PBL as the tumor cells resembled plasmablasts and they were positive for CD138 but negative for CD3, CD20, CD30, CD45, CK7, and CK20 so that the first pathologist gave the diagnosis of PBL. But we found that the tumor cells lack cytoplasmic immunoglobulin light chains, either of kappa or lambda. In addition, the tumor cells were positive for AE1/AE3, CK19, PSA and NKX3.1, indicative of metastatic prostatic adenocarcinoma. [Sukpanichnant et al, 2022] Figures 1 and 2 are two more examples to illustrate problems to diagnose PBL in daily practice.

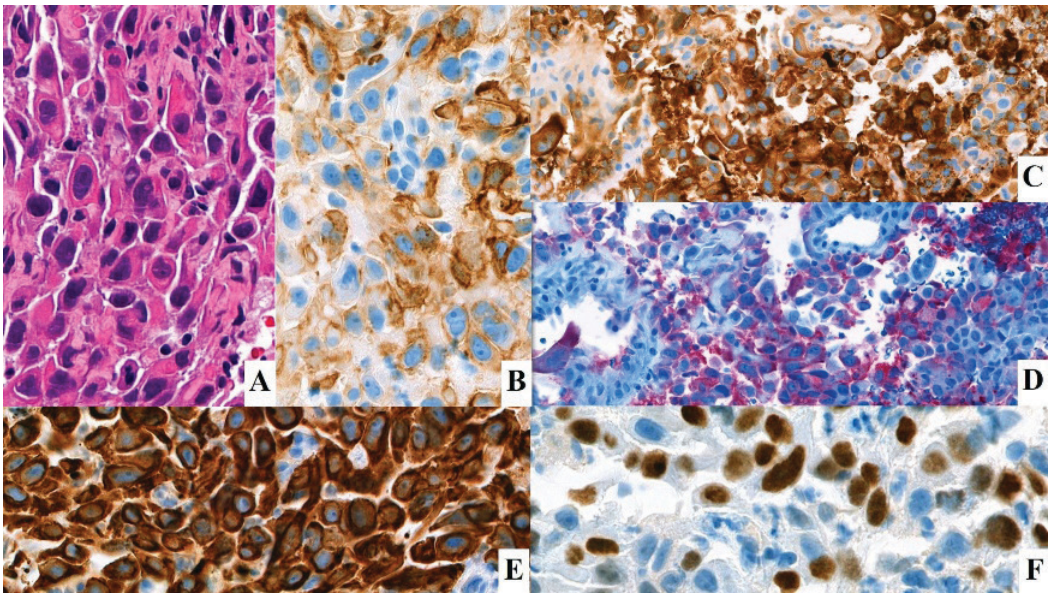


Figure 1 Metastatic carcinoma with squamous differentiation mimicking plasmablastic lymphoma. The tumor cells resemble plasmablasts (A) with CD138 expression (brown colored membranous staining) (B). Non-specific cytoplasmic staining at the rim of the tissue sections for kappa light chain (brown color) (C) more than lambda light chain (red color) (D). Note reactive plasma cells should not have tumor cell morphology like those seen with lambda light chain. The tumor cells are in fact carcinoma cells with AE1/AE3 positivity (brown colored cytoplasmic staining) (E) and squamous differentiation with p40 positivity (brown colored nuclear staining) (F).

The first example is metastatic carcinoma with squamous differentiation mimicking PBL. The tumor cells are positive for CD138 and questionable restriction to cytoplasmic immunoglobulin kappa light chain. However, upon the review, it is non-specific cytoplasmic staining for both kappa and lambda light chains as the reactive plasma cells should not have tumor cell morphology. The tumor cells are in fact positive for AE1/AE3 and p40 protein, indicative of squamous differentiation (Figure 1). The second example is PBL lacking CD38 and CD138 expression but the lymphoma cells express MUM1 protein, MYC protein, restriction to cytoplasmic immunoglobulin lambda light chain, and positivity for in situ hybridization for EBV-encoded small RNA (EBER) (Figure 2). [Note: All these 2 examples were presented partly in the lecture on "Update in WHO classification of Lymphoid Neoplasm 2022" by the author on May 9, 2023 in the 8th International Symposium and the 61st Annual Meeting of TSH (TSH-IS Bangkok 2023) organized by the Thai Society of Hematology (TSH).]

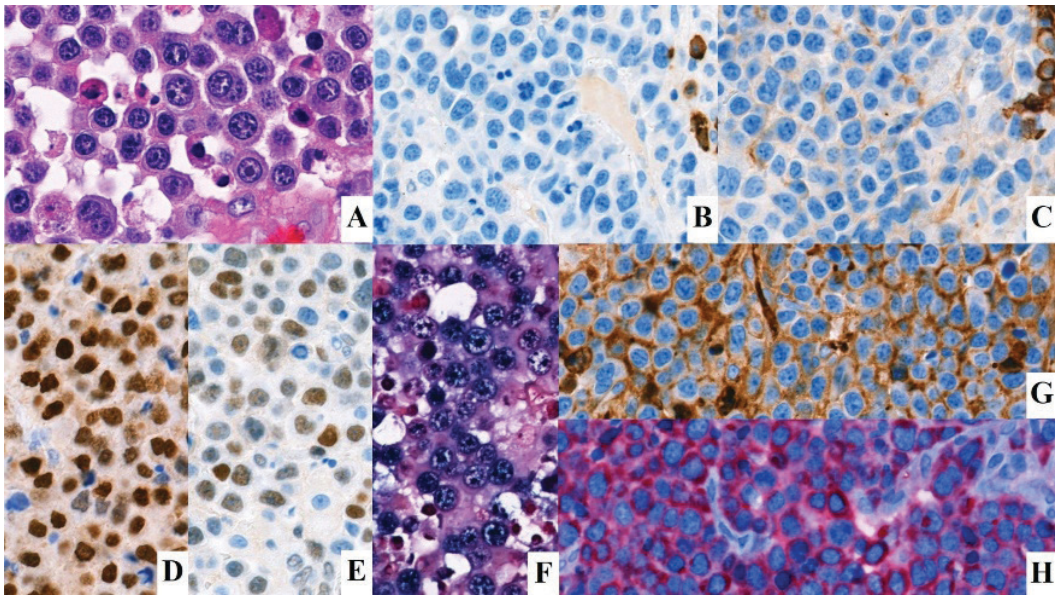


Figure 2 Plasmablastic lymphoma lacking CD38 and CD138 expression. The lymphoma cells are plasmablastic or immunoblastic (A) but they lack expression of CD38 (B) and CD138 (C) while a few small reactive plasma cells along the right margin shows brown colored membranous staining with both CD38 and CD138. However, the lymphoma cells express MUM1 (brown colored nuclear staining) (D) and MYC protein (brown colored nuclear staining) (E). They are also EBER+ (blue colored nuclear staining). The lymphoma cells lack cytoplasmic kappa light chain (no brown colored cytoplasmic staining) (G) but express cytoplasmic lambda light chain (red colored cytoplasmic staining (H). Note a few small reactive plasma cells along the margins of the bottom half show brown colored cytoplasmic staining.

How to diagnose lymphoma

The following are the reflections on how to diagnose lymphoma.

1) Clinical information is very important to distinguish reactive states of the lymph node from lymphoma. It is well documented that some drug reactions can produce lymph node changes mimicking lymphoma. Pathologists should know about any clinical history of drug administration causing lymphoproliferative disorders (LPD), especially immunosuppressive drugs. Careful clinical history taking about immunodeficiency states from any causes is also important. (Ngamdamrongkiat et al, 2022; Sukpanichnant, 2022). Spectrum of tissue changes in drug reaction and immunodeficiency states varies from lymphoid hyperplasia of any types, polymorphic LPD, EBV mucocutaneous ulcer, and frank lymphoma seen in the immunocompetent patients (WHO Classification of Tumours Editorial Board, 2022). The importance of recognizing immunodeficiency states or immune dysregulation is that all the tissue changes described above, even frank lymphoma, may regress by reduction or discontinuation of immunosuppressive drugs (Swerdlow et al, 1993; Ngamdamrongkiat et al, 2022; Sukpanichnant, 2022; WHO Classification of Tumours Editorial Board, 2022).
2) Pathologists should recognize various kinds of tissue reaction in the lymph node and extranodal tissue in order to distinguish them from lymphoma (Swerdlow et al, 1993; Tzankov & Dirnhofer, 2018; Sukpanichnant, 2022). The most common approach is pattern of lymph node changes depending on the compartment of lymph node affected (pattern-based approach) (Tzankov & Dirnhofer, 2018). The other common approach is reactive state- or lymphoproliferation-based as listed in the beta version of the WHO-HAEM5 as tumor-like lesions with B-cell or T-cell predominance; the former includes IgG4-related disease and Castleman disease (unicentric, idiopathic multicentric, or KSHV/HHV8-associated multicentric) while the latter includes Kikuchi-Fujimoto disease and Autoimmune lymphoproliferative syndrome (WHO Classification of Tumours Editorial Board, 2022). In fact, pathologists should recognize not only those listed in the WHO-HAEM5 but also others diseases/reactive states such as infectious mononucleosis, HIV-related lymphadenopathy, syphilitic lymphadenitis, drug-induced lymphadenopathy, immune deficiency/dysregulation LPD (the so-called iatrogenic-associated LPD), immunoblastic lymphadenopathy (polyclonal immunoblastic proliferation), progressive transformation of germinal centers, lymphadenopathy in autoimmune diseases (rheumatoid arthritis or systemic lupus erythematosus), and inflammatory pseudotumor of the lymph node (Swerdlow et al, 1993; Tzankov & Dirnhofer, 2018; Sukpanichnant, 2022).

3) Excision of the whole enlarged lymph node or extranodal lesion is ideal for pathologic evaluation and there is no doubt that it is far much better than core needle biopsy or fine needle aspiration/biopsy (Syrykh et al, 2022). Nevertheless, physicians should keep in mind that any lymph node or lesion larger than 1 cm. needs good logistics and attention from pathologist or pathology laboratory personnel to handle the tissue specimen properly. The most commonly used formalin fixative needs time to fix the tissue (1 mm. per 1 hour) so that it needs approximately 5 hours to completely fix the 1 cm. thick tissue with the hope that the cells located in the very center of the tissue are still intact and preserved well after formalin fixation. Pathologists often observe poor immunostaining results in the center of any large mass without proper handle when compared to the peripheral part of the tissue. A precise pathologic evaluation needs a proper handling of the tissue sample so that the histologic sections and immunostaining are in good quality (Sukpanichnant, 2022).
4) At present, physicians and patients prefer core needle biopsy so that it is very challenging for pathologists to excel skills, knowledge, and experience in order to reach a definitive diagnosis of lymphoma. Certainly, it needs good histologic sections without distortion artefacts. Usually core needle biopsy does not have problem with improper fixation unless the lesion itself has tissue necrosis. Physicians should take care of the tissue quality by applying a proper apparatus and technic to perform a good core needle biopsy to avoid distortion artefacts. Importantly, physician should submit fresh representative tissue for flow cytometry and microbiological studies to provide additional important information about immunophenotyping of the lymphoid cells and microbiological studies for any possible microorganisms (Ingersoll et al, 2019; Sukpanichnant, 2022).
5) Good histologic sections and a proper panel of immunostaining are important to diagnose lymphoma especially in the core needle biopsy (Ingersoll et al, 2019; Cho, 2022; Sukpanichnant, 2022). Limitation, however, occurs in small B-cell lymphoid neoplasm under a difficult situation when reactive states are in differential diagnosis because aberrant expression of some T-cell associated antigens (e.g., CD5 or CD43) in the small B-cells or restriction to cytoplasmic immunoglobulin light chain (kappa or lambda) in the admixed plasma cells may not be detected. Flow cytometry is the technic to demonstrate restriction to surface immunoglobulin light chain that is impossible to detect in paraffin section immunostaining. PCR test to detect clonal rearrangement of immunoglobulin genes is another way to prove monoclonality and support the diagnosis of small B-cell lymphoid neoplasm (Ingersoll et al, 2019; Sukpanichnant, 2022). Recognition of blastic/blastoid nuclear

feature (fine nuclear membrane, fine nuclear chromatin with/without nucleolus) is important to include immunostaining for immature lymphoid phenotype such as TdT or CD34 for lymphoblastic lymphoma or misdiagnosis of this particular entity as other mature lymphoma (Ingersoll et al, 2019; Cho, 2022; Sukpanichnant, 2022).

6) Periodic acid Schiff (PAS) stain helps detecting any glycogen and mucopolysaccharides so that it highlights basement membrane, vasculature, mucin content in glandular epithelial cells, and abnormal PAS+ materials, especially Dutcher-Fahey bodies (PAS+ intranuclear inclusions) in plasma cells that can be found in any B-cell neoplasm with plasmacytic differentiation. PAS is very helpful to complete histologic evaluation in addition to a good H&E-stained slide (Sukpanichnant, 2022).
7) In most cases of lymphoma, the first panel of immunostaining should include at least CD3, CD20, CD30, and Ki-67 for distinction between Hodgkin lymphoma and NHL and for determination of the proliferation index of lymphoma cells by Ki-67. The predominant cell population may represent the lymphoma cells but it is not always true. Background of many small reactive T-cells can be present at times while the scattered worrisome large B-cells need to distinguish between reactive activated/transformed B-cells and large lymphoma cells. It is quite challenging to determine the lymphoma cells using the neoplastic cell behavior (mass, infiltrative, or destructive lesion) and immunostaining panel to establish monoclonality of the lymphoma cells.
8) It is very uncommon for T-cell lymphoma with small cell morphology except for T lymphoblastic lymphoma/leukemia (already mentioned above in #5). One may try immunostaining to show aberrant expression of common T-cell markers, including CD2, CD3, CD5, CD7, and a preferential T-cell marker (CD43). Demonstration of T-cell receptor (TCR)-gamma or TCR-delta is quite abnormal for reactive T-cells so that any lesion with TCR-gamma or TCR-delta may support the diagnosis of T-cell lymphoma (Jaffe, 2019).
9) Partial involvement of the lymph node by lymphoma is possible to see from time to time. Nevertheless, pathologists need to discuss with physicians to exclude other reactive states already mentioned above. In case of doubt, consider to use DNA extraction from the paraffin-embedded tissue remaining in the tissue block for PCR tests to determine clonal rearrangements of immunoglobulin genes and TCR genes (Jaffe, 2019). If the molecular genetic technic is not available, bone marrow examination may be helpful to demonstrate marrow involvement by the lymphoma cells. If marrow evaluation for lymphoma is negative, then close follow-up and rebiopsy of any enlarged lymph node are highly recommended for making a definitive diagnosis of lymphoma.

How to classify lymphoma

The following are the reflections on how to classify lymphoma.

1) By morphology alone at low magnification, good histologic sections should allow appreciation of nodular or diffuse appearance of lymphoma cell proliferation. Nodular growth should raise the concern of a number of specific entities of lymphoma (Table 1). Similarly, diffuse growth also raises the possibilities of many entities of lymphoma (Table 2). In daily practice, one will find out that sometimes PAS stain or immunostaining helps to appreciate the growth pattern better than H&E stain.

Table 1 Nodular growth pattern and list of some specific entities of lymphoma

Follicular lymphoma: Typically small nodules, crowded or back-to-back; may coalesce to form larger but vague nodules (Figures 3A, 3B & 3C).
Small lymphocytic lymphoma/chronic lymphocytic leukemia: Vague nodules (pseudofollicles) (Figure 3D) with pale center accumulation of medium and medium to large-sized lymphoid cells or prolymphocytes (proliferation center) (Figures 3E & 3F) surrounded by smaller lymphoid cells with round dense nucleus in the whole background.
Mantle cell lymphoma: Sometimes with vaguely nodular growth by the expansion of small to medium-sized lymphoid cells with cleaved nuclei and small amount of cytoplasm; may have a normal or atretic germinal center in the center creating a mantle zone configuration (Figures 3G & 3H).
Marginal zone lymphoma: Sometimes with vaguely nodular growth by expansion of small to medium-sized lymphoid cells with cleaved nuclei and modest amount of cytoplasm causing "monocytoid" appearance; may have lymphoid follicle in the center with definite mantle layer of small lymphoid cells separating the monocytoid lymphoma cells from the germinal center (Figure
Nodal T follicular helper cell lymphoma, follicular-type: Mixture of areas like follicular lymphoma (see above) but the lymphoma cells are medium-sized and often have clear cytoplasm and the larger nodule like progressive transformation of germinal center (PTGC).

Nodular lymphocyte predominant Hodgkin lymphoma: Typical large nodule, usually larger than PTGC with typical LP cells (larger than centroblasts) but in some cases, the nodule is not as large as conventional one and sometimes it shows irregular shape (serpiginous growth) (Figure 3J).

Nodular sclerosis classic Hodgkin lymphoma (NSCHL): Typical nodule of mixed small lymphoid cells, plasma cells, eosinophils, histiocytes, and occasional abnormal large cells with retracted cytoplasm (lacunar cells), surrounded by cell poor fibrous bands (rarely seen in core needle biopsy) (Figure 3K). 3I).

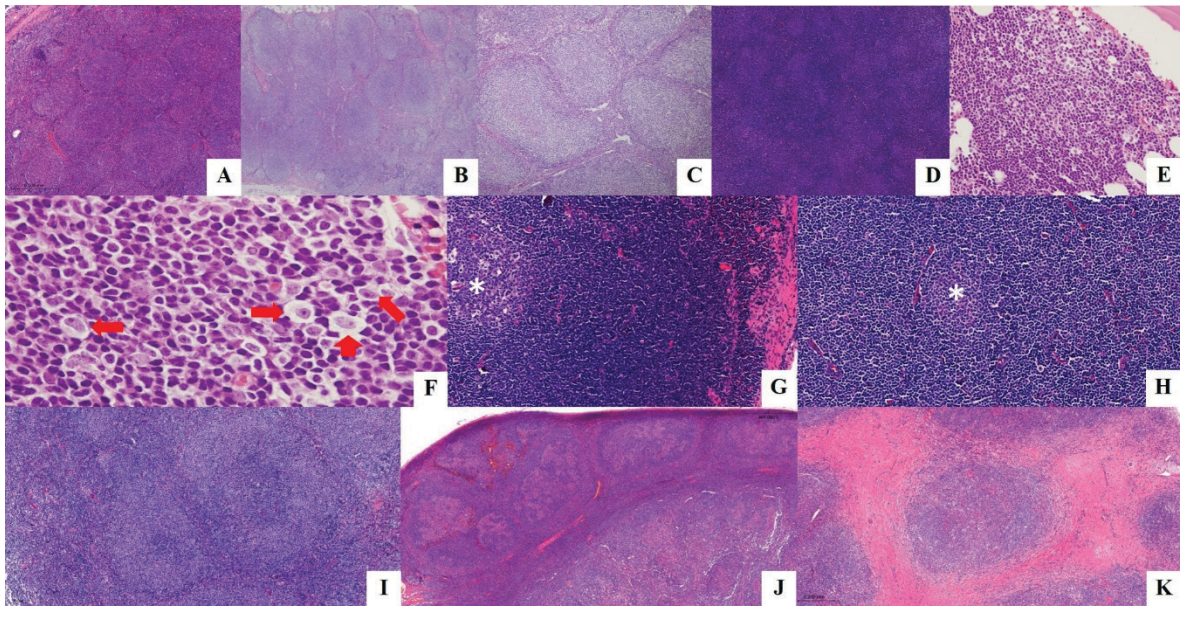


Figure 3 Nodular growths in some specific entities of lymphoma. Crowded nodules in follicular lymphoma (A to C), pseudofollicle (D) and proliferation center (E&F) in small lymphocytic lymphoma/ chronic lymphocytic leukemia (red arrows for prolymphocytes), mantle cell configuration in mantle cell lymphoma (G&H) (asterisks for normal germinal centers), pale nodules in marginal zone lymphoma caused by pale-staining monocytoid lymphoma cells (I), Large nodules with pink and purple colors in nodular lymphocyte predominant Hodgkin lymphoma (J), and a cellular nodule surrounded by thick pink fibrous bands in nodular sclerosis classic Hodgkin lymphoma (K).

Table 2 Diffuse growth pattern and list of some specific entities of lymphoma

Diffuse large B-cell lymphoma (DLBCL): Diffuse growth of medium, medium to large, or large-sized lymphoma cells (Figures 4A & 4B); varying degree of vascularity; sometimes with remaining reactive lymphoid follicle(s); large cells may colonize in the reactive lymphoid follicles (follicular colonization); sometimes replace the normal structure of the underlying tissue; sometimes infiltrate the normal structure in or near the lymphomatous areas (epitheliotropism); sometimes infiltrate the vascular wall with/without angiodestruction and with/without tissue necrosis or ulceration; sometimes with admixed small lymphoid cells with/without admixed epithelioid histiocytes; sometimes with admixed plasma cells (polyclonal in reactive plasma cells but monoclonal in plasmacytic differentiation); sometimes with fibrotic changes of various thickness.

Burkitt lymphoma: Starry-sky pattern within diffuse growth of medium-sized lymphoma cells with some discernible cytoplasm (vacuoles better appreciated under 60x objective lens or oil immersion); note predominance of lymphoma cells as dark blue sky with scattered tangible body macrophages (apoptotic bodies containing) as stars (Figures 4C & 4D).

Nodal T follicular helper cell lymphoma, angioimmunoblastic-type (the so-called "angioimmunoblastic T-cell lymphoma"): Hypervascularity within diffuse growth of polymorphous lymphoid cells varying from small, medium, to large in size with more medium-sized lymphoma cells having clear cytoplasm, usually along the blood vessels with high endothelium (the so-called "high endothelium venules" or "postcapillary venules") with arborization (branching vasculature); occasional large activated/transformed lymphoid cells or immunoblasts, some with larger size resembling Hodgkin cells or Reed-Sternberg cells (Hodgkin-Reed-Sternberg, HRS cells); common to see admixed plasma cells and eosinophils; subcapsular lymph node sinuses can be patent (Figures 4E to 4G).

Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS): Diffuse growth of lymphoma cells, varying from predominantly small pleomorphic cells, mixed small to medium and large-sized lymphoma cells, or large pleomorphic cells; common to see admixed epithelioid histiocytes; sometimes with admixed eosinophils; sometimes with plasma cell infiltration; sometimes with interfollicular growth pattern (T-cell zone distribution) by monotonous medium-sized lymphoma cells (Figures 4H & 4I).

Follicular lymphoma with predominantly diffuse growth pattern: Diffuse growth of small to medium-sized lymphoma cells with cleaved nuclei (centrocytes); occasional larger cells (centroblasts) but not in sheet; may have delicate interstitial fibrotic changes but sometimes with sclerosis (thick fibrous tissue); should not diagnose in core needle biopsy

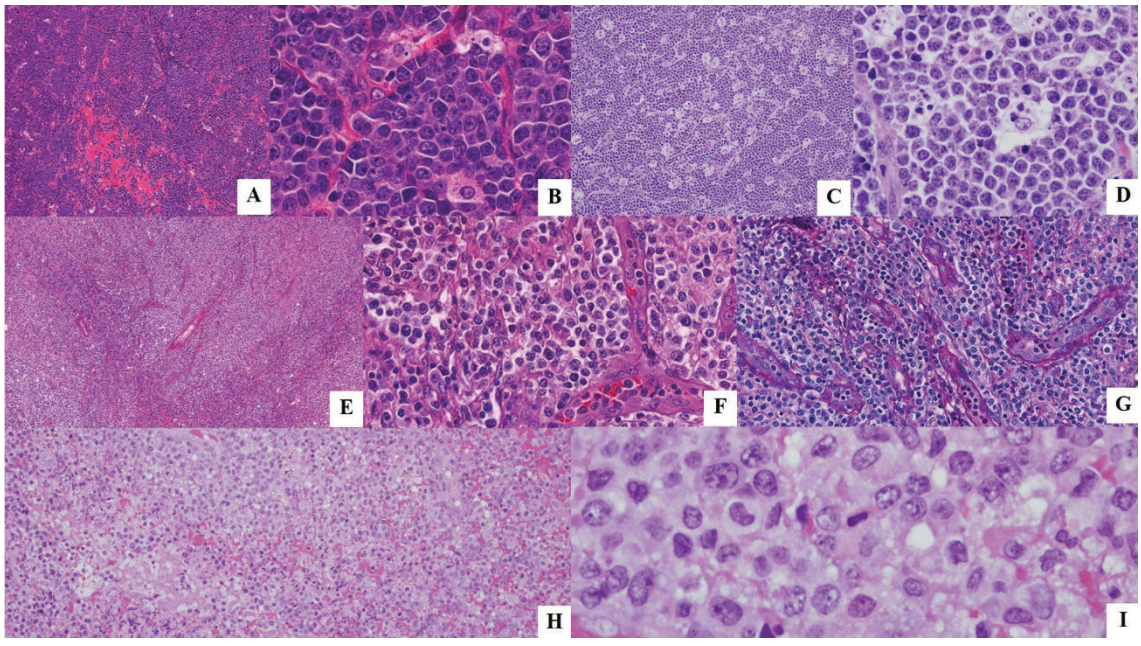


Figure 4 Diffuse growths in some specific entities of lymphoma. Diffuse growth by large lymphoma cells in diffuse large B-cell lymphoma (A&B), starry-sky pattern with monotonous proliferation of medium-sized lymphoma cells in Burkitt lymphoma (C&D), typical diffuse growth with hypervascularity and admixed lymphoma cells with clear cytoplasm in nodal T follicular helper cell lymphoma, angioimmunoblastic-type (E to G; G with PAS stain), and diffuse growth with pleomorphic medium to large-sized lymphoma cells in peripheral T-cell lymphoma, not otherwise specified (H&I).

2) It is important to make sure that the lesion is lymphoma. The lymphoma cells should demonstrate a clear immunophenotype – B-cell, T-cell, NK cell, or Hodgkin-Reed-Sternberg (HRS) cell. If the immunophenotype of lymphoma cells can be established, classifying lymphoma should not be a problem. Nevertheless, to obtain a definite immunophenotype of the lymphoma cells is sometimes very difficult, especially in the core needle biopsy. Sequence of immunostaining order is very important to obtain information for making decision about the immunophenotype of the lymphoma cells. For example, if the panel of immunostaining is limited to CD3, CD20, and CD30 only, then the results show many large CD20+ B-cells in this particular aggregate with occasional admixed apoptotic bodies containing macrophages. It is very important to distinguish this aggregate of large B-cells between reactive germinal center or aggregate of large lymphoma cells. At least 7 unstained slides for further immunostaining should be prepared at the time of cutting slides for the first panel of immunostaining above. Then, immunostaining for CD10, BCL2, BCL6, MUM1, and Ki-67 (total of 5 more tests) can be performed for the true nature of this aggregate of large B-cells. If it is a dark zone of reactive

germinal center, then these large cells are positive for CD10, BCL6, and Ki-67 but negative for BCL2 and MUM1. If it is an aggregate of large lymphoma B-cells, then they can be evaluated for cell of origin according to Hans algorithm. Moreover, the other 2 unstained slides can be used for c-myc (MYC protein) and cyclin D1 evaluation if needed.

3) Follow the essential diagnostic criteria given in the WHO-HAEM5 in order to classify lymphoma (WHO Classification of Tumours Editorial Board, 2022) after morphologic evaluation and immunostaining work-up above.

Using an effective approach in morphologic evaluation and even a limited panel of immunostaining, the D&C of lymphoma can be given within an appropriate rapid turnaround time (24-48 hours) under a good clinical correlation (Sukpanichnant, 2022). While targeted therapies improve clinical outcomes since anti-CD20 immuno-therapy in the past 25+ years, advances in diagnostics for lymphoma and sophisticated technics, especially in molecular studies, allow us to better understanding of lymphoma as well as high-throughput workups. The author believes that a good histology is still critical and concurs with Nathwani and colleagues about the important role of histology in conjunction with a good clinical correlation to decide the most effective way to gather information for a better management for individual patient care (Nathwani et al, 2007).

Conclusion

There is no doubt that technology advances lead to better medical treatment and care in history of humankind but along the way, some delays or misunderstandings occur from time to time. The D&C of lymphoma is also an example of such experiences as already shown in the aforementioned reflections but it will get better eventually and that means the present practice using morphologic evaluation and immunostaining will be more precise by more sophisticated technology that provides more useful information for better patient care and quality of life. Anyway, in this interim, there is no guarantee about the benefit of the high-throughput workups over the conventional approach, using morphology and immunophenotype to the D&C of lymphoma with an appropriate rapid turnaround time under a good clinical correlation.

Acknowledgements

The author Sanya Sukpanichnant is supported by Chalermphrakiat Grant, Faculty of Medicine Siriraj Hospital, Mahidol University.

About the Author

Sanya Sukpanichnant. An Associate Fellow of the Royal Society of Thailand and a Professor at Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University. He received his training in hematopathology (1990-1993) from the late Professor Dr. Robert D. Collins, who co-established the Lukes-Collins classification for malignant lymphoma in 1974. His publication focuses not only on lymphoma but also other hematologic diseases (55 and 40 articles in international and national journals, respectively).

References

Cho J. Basic immunohistochemistry for lymphoma diagnosis. Blood Res 2022; 57: 55-61.

Dalla-Favera R, Bregni M, Erikson J, Patterson D, Gallo RC, Croce CM. Human c-myc onc gene is located on the region of chromosome 8 that is translocated in Burkitt lymphoma cells**.** Proc Natl Acad Sci USA 1982; 79: 7824-7827.

Harris NL, Jaffe ES, Stein H, Banks PM, Chan JKC, Cleary ML, Delsol G, De Wolf-Peeters C, Falini B, Gatter KC, Grogan TM, Isaacson PG, Knowles DM, Mason DY, Muller-Hermelink H-K, Pileri SA, Piris MA, Ralfkiaer E, Warnke RA. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84: 1361-1392.

Ingersoll KF, Zhao Y, Harrison GP, Li Y, Yang LH, Wang E. Limited tissue biopsies and hematolymphoid neoplasms. Am J Clin Pathol 2019; 152: 782-798.

Intragumtornchai T, Bunworasate U, Wudhikarn K, Lekhakula A, Julamanee J, Chansung K, Sirijerachai C, Norasetthada L, Nawarawong W, Khuhapinant A, Siritanaratanakul N, Numbenjapon T, Prayongratana K, Chuncharunee S, Niparuck P, Suwanban T, Kanitsap N, Wongkhantee S, Pornvipavee R, Wong P, Makruasi N, Wannakrairot P, Assanasen T, Sukpanichnant S, Boonsakan P, Kanoksil W, Ya-In C, Kayasut K, Mitranun W, Warnnissorn N. Non-Hodgkin lymphoma in South East Asia: An analysis of the histopathology, clinical features, and survival from Thailand. Hematol Oncol 2018; 36: 28-36.

Jaffe ES. Diagnosis and classification of lymphoma: Impact of technical advances. Semin Hematol 2019; 56: 30-36.

Jaffe ES, Harris NL, Stein H, Vardiman J. eds. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2001.

Kind S, Merenkow C, Büscheck F. Prevalence of syndecan-1 (CD138) expression in different kinds of human tumors and normal tissues. Disease Markers 2019; Article ID 4928315, 11 pages https://doi.org/10.1155/2019/4928315

Lennert K, Stein H, Kaiserling E. Cytological and functional criteria for the classification of malignant lymphomata. Br J Cancer 1975; 2 Suppl: 29-43.

Lukes RJ, Collins RD. Immunologic characterization of human malignant lymphomas. Cancer 1974; 34(4 Suppl): 1488-1503.

Nathwani BN, Sasu SJ, Ahsanuddin AN, Hernandez AM, Drachenberg MR. The critical role of histology in an era of genomics and proteomics: a commentary and reflection. Adv Anat Pathol 2007; 14: 375-400.

National Cancer Institute. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. The Non-Hodgkin's Lymphoma Pathologic Classification Project. Cancer 1982; 49: 2112-2135.

Natkunam Y, Warnke RA, Montgomery K, Falini B, van de Rijn M. Analysis of MUM1/IRF4 protein expression using tissue microarrays and immunohistochemistry. Mod Pathol 2001; 14: 686-694.

Ngamdamrongkiat P, Arromdee E, Vongwiwatana A, Owattanapanich W, Sukpanichnant S. Histopathological and Clinical Features of Methotrexate-Associated Lymphoproliferative Disorders and Post-Transplant Lymphoproliferative Disorders. Siriraj Medical Journal 2022; 74: 575-589.

Pongpruttipan T, Sukpanichnant S, Assanasen T, Wannakrairot P, Boonsakan P, Kanoksil W, Kayasut K, Mitarnun W, Khuhapinant A, Bunworasate U, Puavilai T, Bedavanija A, Garcia-Herrera A, Campo E, Cook JR, Choi J, Swerdlow SH. Extranodal NK/T-cell lymphoma, nasal type, includes cases of natural killer cell and $\alpha\beta$, $\gamma\delta$, and $\alpha\beta/\gamma\delta$ T-cell origin: a comprehensive clinicopathologic and phenotypic study. Am J Surg Pathol 2012; 36: 481-499.

Rappaport H. Tumors of the hematopoietic system. In: Atlas of Tumor Pathology, Vol. Section III (Series I ed). Washington, DC: Armed Forces Institute of Pathology; 1966.

Reed DM. On the pathological changes in Hodgkin's disease with special reference to its relation to tuberculosis. Johns Hopkins Hosp Rep 1902; 10: 133-198.

Sitthinamsuwan P, Pattanaprichakul P, Treetipsatit J, Pongpruttipan T, Sukpanichnant S, Pincus LB, McCalmont TH. Subcutaneous Panniculitis-Like T-Cell

Lymphoma Versus Lupus Erythematosus Panniculitis: Distinction by Means of the Periadipocytic Cell Proliferation Index. Am J Dermatopathol 2018; 40: 567-574.

Stansfeld AG, Diebold J, Noel H, Kapanci Y, Rilke F, Kelényi G, Sundstrom C, Lennert K, van Unnik JA, Mioduszewska O, Wright DH. Updated Kiel classification for lymphomas. Lancet 1988; 1: 292-293.

Sukpanichnant S. Analysis of 1,983 cases of malignant lymphoma in Thailand according to the WHO classification. Hum Pathol 2004; 35: 224-230.

Sukpanichnant S. Malignancy of the lymph node: how general practitioners and pathologists can achieve a definitive diagnosis. Siriraj Medical Journal 2022; 74: 604-617.

Sukpanichnant S, Jindamai Y, Kookasemkij P. Metastatic prostatic adenocarcinoma mimicking plasmablastic lymphoma: diagnostic pitfalls. Asian Archives of Pathology 2022; 4: 29-40.

Sukpanichnant S, Sonakul D, Piankijagum A, Wanachiwanawin W, Veerakul G, Mahasandana C, Tanphaichitr VS, Suvatte V. Malignant lymphoma in Thailand. Changes in the frequency of malignant lymphoma determined from a histopathologic and immunophenotypic analysis of 425 cases at Siriraj Hospital. Cancer 1998; 83: 1197-1204.

Sukpanichnant S, Udomsakdi-Auewarakul C, Ruchutrakool T, Leelakusolvong S, Boonpong-manee S, Chinswangwatankul V. Gastrointestinal lymphoma in Thailand: a clinicopathologic analysis of 120 cases at Siriraj Hospital according to WHO classification. Southeast Asian J Trop Med Public Health 2004; 35: 966-976.

Sundberg RD. Lymphocytogenesis in human lymph nodes. J Lab Clin Med 1947; 32: 777-792.

Swerdlow SH, Sukpanichnant S, Glick AD, Collins RD. Reactive states in lymph nodes resembling lymphomas or progressing to lymphomas. A selective review. Mod Pathol 1993; 6: 378-391.

Syrykh C, Chaouat C, Poullot E, Amara N, Fataccioli V, Parrens M, Traverse-Glehen A, Molina T-J, Xerri L, Martin L, Dubois R, Lacheretz-Szablewski V, Copin M-C, Moreau A, Chenard M-P, Cabarrou B, Lusque A, Gaulard P, Brousset P, Laurent C. Lymph node excisions provide more precise lymphoma diagnoses than core biopsies: a French Lymphopath network survey. Blood 2022; 140: 2573-2583.

Taub R, Kirsch I, Morton C, Lenoir G, Swan D, Tronick S, Aaronson S, Leder P.

Translocation of the c-myc gene into the immunoglobulin heavy chain locus in human Burkitt lymphoma and murine plasmacytoma cells. Proc Natl Acad Sci USA 1982; 79: 7837-7841.

Taylor CR and Hartsock RJ. Classifications of lymphoma; reflections of time and technology. Virchows Arch 2011; 458: 637-648.

Tzankov A and Dirnhofer S. A pattern-based approach to reactive lymphadenopathies. Semin Diagn Pathol 2018; 35: 4-19.

Vangveeravong S, Sukpanichnant S, Uiprasertkul M, Khuhapinant A, Singalavanija T. Clinical Characteristics and Treatment Outcomes of Patients with Primary Ocular Adnexal Lymphoma at Siriraj Hospital. Siriraj Medical Journal 2022; 74: 865-873.

WHO Classification of Tumours Editorial Board. Haematolymphoid tumours [Internet; beta version ahead of print]. Lyon (France): International Agency for Research on Cancer; 2022 [cited 2023 April 17]. (WHO classification of tumours series, 5th ed.; vol.11). <https://tumourclassificatioin.iarc.who.int/chapters/63>

Revisiting Diabetic Polyneuropathy and Autonomic Neuropathy

Kongkiat Kulkantrakorn[1,2]

Abstract

Polyneuropathy is the common complication from diabetes mellitus (DM). It can lead to more severe disabilities such as neuropathic pain, imbalance, chronic wound, and amputation. Distal symmetric sensorimotor axonal polyneuropathy is the most common form and sometimes coexists with autonomic neuropathy. Routine screening during regular clinic visit is a must for early diagnosis. Many pathogenetic pathways were described and may lead to better prevention and treatment. Currently, optimization of glucose control and management of other vascular risk factors are recommended. Both pharmacological and non-pharmacological measures are available for symptomatic treatment and may modify disease progression. Further understanding in this disease will help in improving the patient's outcomes.

Keywords: diabetes mellitus; polyneuropathy; neuropathic pain; autonomic neuropathy

Introduction

Diabetes mellitus (DM) is the most common cause of peripheral neuropathy worldwide. There are many forms of diabetic neuropathy which represents disorders in nerve root (radiculopathy), plexus (plexopathy), individual nerve (mononeuropathy) and many nerve throughout the body (polyneuropathy).

Polyneuropathy is the common complication from DM. It can lead to more severe disabilities such as neuropathic pain, imbalance, chronic wound, and amputation. Distal symmetric sensorimotor axonal polyneuropathy (DSPN) is the most common form which is easily to diagnose, potentially preventable and treatable. While autonomic neuropathy often manifests as debilitating systemic symptoms which make it harder

[1] Department of Internal Medicine, Faculty of Medicine, Thammasat University, Pathumthani, Thailand.
[2] The Academy of Science, The Royal Society of Thailand, Bangkok, Thailand.

Correspondence to Kongkiat Kulkantrakorn (MD), Department of Internal Medicine, Faculty of Medicine, Thammasat University, Pathumthani, Thailand. Email: kongkiat1@gmail.com

to recognize and manage. Sometimes, both conditions coexist. In this article, both DSPN and autonomic neuropathy which are of interest will be comprehensively reviewed for the audience to better understand these well-established conditions.

Patterns of diabetic neuropathy

Several different patterns of neuropathy can present in individuals with diabetes. Of these, the most common is distal sensorimotor polyneuropathy (DSPN). Examples of patterns of neuropathy are DSPN, small fiber neuropathy, treatment-induced neuropathy, radiculoplexopathy or radiculopathy, mononeuropathy, and autonomic neuropathy or treatment-induced neuropathy (Feldman et al, 2019).

Small fiber neuropathy has the same distribution as DSP, although the neurological examination and results from nerve conduction velocity studies are different. Diabetic radiculoplexopathy or radiculopathy often present with acute or subacute severe focal limb pain and follow by weakness. It can respond to immuno-therapy and usually improves with time, unlike other types of nerve injury in individuals with diabetes.

Treatment-induced neuropathy or insulin neuritis is under-recognized. It is caused by overaggressive glycemic control or rapid reduction of glucose level from insulin and can manifest with generalized body and limb pain without clear weakness. In this article, the common forms which are DSPN and autonomic neuropathy will be discussed.

Distal sensorimotor polyneuropathy (DSPN)

DSPN is the most common form of diabetic complication involving peripheral nervous system. This condition manifests as a symmetrical, length dependent, sensorimotor polyneuropathy and results from impaired metabolism and microcirculation after exposure to chronic hyperglycemia and other cardiovascular risk factors. It is associated with other cardiovascular risk factors such as obesity, diabetic duration, age, inadequate blood sugar control, smoking, etc. DSPN is commonly associated with autonomic involvement, might commence insidiously and if intervention is not successful, it becomes progressive and chronic (Feldman et al, 2019; Ziegler et al, 2022).

It is quite intriguing that DSPN had different manifestation in each patient. Some of them had severe pain which coincide with sensory deficit, while some of them are asymptomatic and may present with painless foot ulcer. The impaired sensory perception is associated with loss of protective mechanisms from pain or injury. This injury-prone condition eventually causes diabetic foot ulcer and may lead to limb amputation. Therefore, early recognition and management is crucial in routine diabetic care.

Nevertheless, DM patients often have coexisting diseases and are prone to have other causes of neuropathy. Additional clinical information and investigations should also be done for differential diagnosis such as medication side effects, uremia, vitamin B12 deficiency, hypothyroidism, monoclonal gammopathy, etc. The initial laboratory testing package should include complete blood count, thyroid function test, vitamin B12 level, serum immunofixation electrophoresis and other routine blood chemistry (England et al, 2009). Autonomic testing and other additional investigations may be required in some cases (England et al, 2009).

In 2007 survey in Thailand, involving 1078 DM patients in primary care health clinic, showed peripheral neuropathy prevalence of 34%. It is the most common complication from DM and might explain the high rate of foot ulcers in this cohort (Nitiyanant et al, 2007). Routine practice of regular assessment for potential complications are not performed adequately. Among Asian countries, the prevalence is in the range of 33-58 % depending on screening tools (Nitiyanant et al, 2007; Ferrario et al, 2013). Finally, it leads to burden and cost to the society (Malik et al, 2009). Regrettably, it is often underdiagnosed or misdiagnosed because of low awareness amongst both patients and physicians. Furthermore, crude screening tools, such as the 10-g mono-filament, can detect only for large fiber polyneuropathy and is often positive only in severe neuropathy. Moreover, it is often normal is small fiber neuropathy which will lead to false diagnosis.

Diagnosis and screening

The diagnosis of DSPN is quite straightforward. It requires a diabetic history, neuropathy signs and symptoms, abnormal screening test and exclusion of other causes of neuropathy. The Toronto consensus criteria can further define the level of certainty of diagnosis to possible, probable and confirmed DSPN depending on the evidence and confirmatory test. If possible, nerve conduction studies should be done to characterize the type and severity of polyneuropathy. In research setting, quantitative sensory testing and intra-epidermal nerve fiber density from skin biopsy are helpful for objective measurement (Feldman et al, 2019; Ziegler et al, 2022; England et al, 2009; ElSayed et al, 2023). Regarding the diagnosis of neuropathic pain, Thai neuropathic pain guideline recommended Thai DN4 questionnaire (Thai version of Neuropathique 4 Questionnaire) for screening and diagnosis of neuropathic pain.

American Diabetic Association (ADA) recommended that all diabetic patients should be assessed for DSPN starting diagnosis of type2 DM, 5 years after diagnosis of type1 DM and at least annually thereafter. Screening patient with prediabetes who

have symptoms of DSPN should also be considered because up to 50% of DSPN cases may be asymptomatic. The screening protocol includes testing of large nerve fiber function using 128 Hz tuning fork or 10 g-monofilament, tendon reflexes and testing of small nerve fiber function using pin prick sensation or temperature perception. All DM patients should have annual 10 g monofilament to identify feet at risk for ulceration and amputation. Foot inspection and peripheral arterial disease assessment can also be performed during the same time (ElSayed et al, 2023; Nkonge et al, 2023).

Painful diabetic neuropathy (PDN)

Around one fourth of patients have pain associated with neuropathy, so called : painful diabetic neuropathy (PDN). This pain is quite debilitating and associated with impaired quality of life and long-term disability. The study from a tertiary care center in Thailand showed lower quality of life, especially in physical domains when compared to healthy Thai population. Moreover, the degree of severity is similar to diabetic foot ulcer and other neurological illnesses (Kulkantrakorn & Lorsuwansiri, 2013).

The pain in PDN is quite interesting. Positive symptoms (such as spontaneous pain, allodynia, hyperalgesia, paresthesia) and negative sensory symptoms (such as anesthesia, hypoalgesia) may paradoxically coexist. The intensity of pain is in moderate range in visual analog scale. Regarding pain characteristics, sharp pain, surface pain, burning pain are more severe than other types of pain. This pain pattern profile is different among each patient and it may aid in medication selection and monitoring (Ziegler et al, 2021). Regarding the diagnosis of neuropathic pain, Thai neuropathic pain guideline recommended Thai DN4 questionnaire (Thai version of Neuropathique 4 Questionnaire) for screening and diagnosis of neuropathic pain.

Pathogenesis

Multifactorial factors were proposed in the pathogenesis. The well-known ones are hyperglycemia and microvascular etiologies. Chronic hyperglycemia leads to increased reactive oxygen species which leads to oxidative stress, mitochondrial dysfunction. Activation of protein kinase C, polyol pathway, protein kinase C and advanced glycation end-products pathways, along with hyperinsulinemia will further worsen inflammatory process manifesting as cytokines/chemokines production from inflammation and final apoptosis. Regarding microvascular hypothesis, dyslipidemia and inflammatory cascade cause the impairment of microvascular circulation in nearby nerve environment. It will cause nerve ischemia or infarction and further enhance genetic abnormalities and inflammatory vicious cycle (Feldman et al, 2019; Ziegler et al, 2022; Ziegler et al, 2021).

Treatment

Pathogenetic based treatment

Several compounds in various groups were investigated but many of them were unsuccessful such as aldose reductase, inhibitors, prostacyclin analogs, nerve growth factors, vascular endothelial growth factor, protein kinase C inhibitors, vitamin E, etc.

Alpha lipoic acid which reduce oxidative stress had more extensive studies showing benefit in symptomatic relief and may counteract the PDN pathogenesis. It is initially tested with intravenous formulation and later with oral formulation. Most are short term studies which showed significant pain reduction , based on various measures. It may slow down the disease progression, based on one large long-term study of four-year duration. It has been registered as an approved medication in this indication in many countries and it is also available as nutritional supplement. Recent studies showed promising data of new aldose reductase inhibitors (epalrestat, ranirestat), alpha lipoic acid and benfotiamine. Further studies are underway for short- and long-term efficacy and safety information (Ziegler et al, 2021; Abubaker et al, 2022).

Benfotiamine is also another interesting alternative. It is a synthetic prodrug of thiamine with rapid and excellent absorption. It activates transketolase activities and finally inhibits AGE formation. Many diabetic patients with coexisting diseases such as malnutrition or chronic renal failure may have subclinical thiamine deficiency and they are prone to have polyneuropathy from nutritional deficiency. Benfotiamine at the dose of 300-600 mg/d has been shown in short-term studies to reduce neuropathic pain. It may be combined with other medications without significant side effects. Their side effects are comparable to placebo group. Both carry no significant interaction with other drugs or underlying diseases. Long-term studies are being performed (Ziegler et al, 2021). Recent meta-analysis concluded that B vitamins should be considered a plausible therapy for diabetic neuropathy, but its overall efficacy remains uncertain and requires further study (Karaganis & Song, 2021).

Symptomatic treatment for painful diabetic neuropathy

Assessment of pain and its effect on function and quality of life should be performed before any treatment. When initiating pharmacologic intervention for PDN, clinicians should counsel patients that the goal of therapy is to reduce, and not necessarily to eliminate, pain. Clinicians should assess patients with PDN for the presence of concurrent mood and sleep disorders and treat them as appropriate. Individualized approach is recommended to use may factors for drug selection, such

as comorbidities, concurrent medication and potential drug interaction, cost, mood or sleep disorders, fall risk, etc. Clinicians may assess patient preferences for effective oral, topical, nontraditional, and nonpharmacologic interventions for PDN (ElSayed et al, 2023; Ziegler et al,2021; Price et al, 2022).

Several groups of medications have been shown in clinical trials to aid in relieving this debilitating pain condition. In many national and international guidelines, gabapentinoids (such as gabapentin, pregabalin, mirogabalin), serotonin-norepinephrine reuptake inhibitors (such as duloxetine, venlafaxine, desvelafaxine), tricyclic antidepressants (such as amitriptyline, nortriptyline) are recommended as first-line pharmacologic treatments for neuropathic pain in diabetes. The second-line medications may include sodium channel blockers (such as oxcarbazepine, lamotrigine, lacosamide, valproic acid), weak opioid (tramadol) and topical capsaicin preparations. Due to high teratogenic potential from valproic acid in women of childbearing potential, clinicians should not recommend valproic acid unless multiple other medications have failed (Feldman et al, 2019 & Ziegler et al, 2022 & Ziegler et al, 2021; Price et al, 2022; Moisset et al, 2020).

Strong opioids should not be used due to their potential serious side effects, overdose and addition. Moreover, opioid use in non-malignant indication is strongly related to higher risk of hospitalization and death from overdose. The use of opioid along with sedatives, alcohol and some gabapentinoids may elevate this risk. The issue of tolerance, misuse and dependence should be evaluated prior and during the treatment. Regular evaluation should be performed at least every 3 months. Recent guideline also discourages its use and highlight the need for safer medication (Price et al, 2022; Moisset et al, 2020). For the past few years, cannabis has been increasingly used for chronic non cancer pain, which includes neuropathic pain. Mild pain reduction was seen in neuropathic pain trial, but the side effects may outweigh the benefit (Mücke et al, 2018).

In patients preferring topical, nontraditional, or nonpharmacologic interventions, providers may offer topical (capsaicin, glyceryl trinitrate spray, Citrullus colocynthis), nontraditional (Ginkgo biloba) (Price et al, 2022) or nonpharmacologic interventions (CBT, exercise, Tai Chi, mindfulness). Topical analgesic is an important alternative to avoid systemic side effect. Lidocaine patch was recommended as second line treatment , but it is not convenient to use in wide or ill-defined area. The potential of systemic absorption is also a concern.

Capsaicin in a potent agonist of transient receptor potential vanilloid- 1. This receptor is found at skin. Once this receptor is activated, the burning sensation will

be perceived. However, with repetitive application, it will lead to hyperexcitation, mitochondrial dysfunction and degeneration of intraepidermal small nerve fiber. Therefore, various preparations of topical capsaicin have been studied since 1980s. Capsaicin gel or cream at the concentration of 0.075% or 8% patch may be useful and it causes almost no systemic side effect (Kulkantrakorn et al, 2022). Local skin reaction is the major limitation. Lower concentrations in cream and lotion were tested in randomized controlled trial. They did not provide adequate pain relief, but the local reaction is much tolerable (Kulkantrakorn et al, 2013; 2019). High dose patch should not be used in insensate area, and it may impair body self-protective mechanism from pain.

A refer to neurologist or pain specialist when pain control is not achieved within the scope of practice of the treating physician. Physician should advise their patients that a series of medications may need to be tried to identify the treatment that most benefits patients with PDN. Each intervention should be adequately tried to reduce neuropathic pain. Before calling it failure, the patients should be on efficacious dose for approximately 12 weeks is required without significant pain reduction or they experience severe side effect.

If the initial medication does not work well or side effect is not tolerable, other medications from a different effective class should be selected. In partial responders, a trial of a different class as a second monotherapy or combination of different class is recommended (Ziegler et al, 2022). However, potential drug interactions with coexisting medication or underlying disease should be thoroughly examined. Despite widespread use and some combination therapy trials, there is no convincing evidence to suggest superiority of any combination over its respective monotherapies. Therefore, when clinical should closely monitor their patient for their safety and additional benefit (Balanaser et al, 2023).

Regarding opioid treatment, clinicians should not use strong opioids for the treatment of PDN due to its more side effect, potential addiction, and overdose. If patients are currently on opioids or opioids/ SNRI dual mechanism agents (such as tramadol or tapentadol) for the treatment of PDN, clinicians may offer the option of a safe taper off these medications and discuss alternative nonopioid treatment strategies.

In refractory case, botulinum toxin injection has been reported to be helpful, but the procedure itself is painful and costly. Other interventions such as spinal cord stimulation, magnetic stimulation, intrathecal pump or nerve blocks are still under investigation regarding their efficacy and safety (Balanaser et al, 2023).

Regarding the prevention of this condition, glucose control should be optimized to prevent or delay the development of neuropathy in patients with type 1 diabetes and to slow the progression of neuropathy in people with type 2 diabetes. The control of blood pressure and serum lipid can reduce the risk or slow the progression of diabetic neuropathy as well (Feldman et al, 2019; Ziegler et al, 2022).

Table 1 Difference between large and small fiber neuropathy

	Large fiber neuropathy	**Small fiber neuropathy nerve fiber**
Normal function	Pressure, balance, proprioception, deep-seated pain	Nociception, Protective sensation, temperature
Symptoms	Numbness, tingling, poor balance, wasting, weakness	Pain: burning, electric shocks, stabbing Thermal imperception
Physical Examination	Reduced or absent - Ankle reflexes - Vibration perception - 10-g monofilament - Proprioception	Reduced or absent - Pinprick sensation (symmetrical, distal to proximal) - Thermal discrimination

Autonomic neuropathy

Clinical manifestations

Autonomic nervous system involvement, so called autonomic neuropathy, occasionally coexists with small fiber polyneuropathy. It can present with non-specific systemic symptoms due to its control in internal organs (Freeman R, 2020). Again, some of them are asymptomatic and could be diagnosed only with screening tests. Therefore, screening for autonomic dysfunction is recommended in the work up for all polyneuropathy (Price et al, 2022).

Diabetic autonomic neuropathy encompasses a group of disorders caused by impairment of the sympathetic and parasympathetic nervous system. Cardiac autonomic neuropathy (CAN) can present as generalized weakness, light-headedness or frank syncope accompanied by orthostatic tachycardia or bradycardia and exercise intolerance.

Cardiac autonomic neuropathy is the more serious one which is associated with increased overall mortality and sudden death. Most patients initially present with parasympathetic denervation and increase of sympathetic tone leading to resting tachycardia and decreased heart rate variability and impaired exercise tolerance and finally orthostatic hypotension. Orthostatic hypotension is from sympathetic vasomotor denervation causing reduced vasoconstriction of splanchnic and peripheral vascular beds. Heart rate are often increased from vagal neuropathy and later became slow and fixed. Orthostatic blood pressure measurement, heart rate variability test by deep breathing and Valsalva maneuver and tilt table test are recommended as screening tools (Spallone et al, 2019; Benichou et al, 2018).

Genitourinary dysfunction may present as impaired bladder sensation, incomplete bladder emptying and erectile dysfunction. Gastroparesis, post prandial bloating, constipation or profuse watery diarrhea are sometimes seen. Skin manifestation include hypo or hyperhidrosis and gustatory sweating. Early diagnosis and proactive management are the key management strategies. Comprehensive and symptomatic treatment in each symptom will help alleviating the disability and reduce mortality in these patients. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

Symptoms of gastrointestinal autonomic dysfunction (also known as gastroparesis) include nausea, bloating, early satiety with poor appetite, postprandial vomiting, and brittle diabetes (that is, hard-to-control diabetes). Esophageal dysfunction can also occur with dysphagia (difficulty swallowing) for solid foods and heartburn secondary to acid reflux .

Urogenital autonomic neuropathy presents as bladder dysfunction (also known as diabetic cystopathy) that can range from urinary retention with hesitancy to urinary incontinence with urgency. Sexual dysfunction is another common manifestation of urogenital autonomic neuropathy. In men, sexual dysfunction manifests as impotence, decreased libido, and abnormal ejaculation, whereas in women, sexual dysfunction presents as pain during intercourse, poor lubrication and reduced libido. Sudomotor autonomic dysfunction presents as dry skin (anhidrosis) with gustatory sweating.

Diagnosis and screening

ADA also recommended routine screening for symptoms and signs of autonomic neuropathy in patients with microvascular complications. It should be assessed in people with diabetes starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter and with evidence

of other microvascular complications, particularly kidney disease and diabetic peripheral neuropathy. Screening can include asking about orthostatic dizziness, syncope, or dry cracked skin in the extremities. Signs of autonomic neuropathy include orthostatic hypotension, a resting tachycardia, or evidence of peripheral dryness or cracking of skin (ElSayed et al, 2023). Certain investigations and exclusion of other potential etiologies are required prior to the diagnosis of autonomic neuropathy in each organ.

Management of diabetic autonomic neuropathy

The treatment depends on the specific subtype. Optimization of glucose control early in the course of type 1 diabetes mellitus (T1DM) is recommended to prevent or delay CAN, whereas targeting all metabolic risk factors is the recommendation for type 2 diabetes mellitus (T2DM). Volume repletion, physical activity, low-dose fludrocortisone or midodrine and compression stockings are among treatment options for CAN in patients with T1DM or T2DM.

Regarding gastrointestinal autonomic dysfunction, other causes should also be excluded particularly side effects from opioids or diabetic medication (glucagon-like peptide 1 receptor agonists) and other surgical conditions. Metoclopramide can be used for short term symptomatic treatment for gastroparesis. The management of diabetic gastroparesis is guided by the severity of symptoms, the magnitude of delayed GE, and the nutritional status. Initial options include dietary modifications, supplemental oral nutrition, and antiemetic and prokinetic medications. Patients with more severe symptoms may require a venting gastrostomy or jejunostomy and/or gastric electrical stimulation. Promising newer therapeutic approaches include ghrelin receptor agonists and selective 5-hydroxytryptamine receptor agonists (Bharucha et al, 2019).

Routine screening and exclusion of other causes are recommended in patients with urogenital autonomic neuropathy. Pharmacological treatment of male erectile dysfunction includes phosphodiesterase type 5 inhibitors such as sildenafil and tadalafil. Adequate skin moisturizer can provide relief for dry skin and prevention of chronic wound.

Conclusion

Distal symmetric sensorimotor axonal polyneuropathy and autonomic neuropathy are common in diabetic patients. Routine screening during treatment can lead to early diagnosis. Multiple mechanisms are proposed for its pathogenesis. Optimization of glucose control and management of other vascular risk factors are also recommended.

Symptomatic treatment and prevention of complications from neuropathy can lead to better patient's outcome.

About the Authors

Kongkiat Kulkantrakorn is a Professor at the Department of Internal Medicine, Faculty of Medicine, Thammasat University. Currently, he is a Fellow of the Royal Society of Thailand and Director of Thammasat Health Innovation Center. He is a neurologist, specializing in neuromuscular medicine. His research and clinical interests include neuromuscular disease, geriatric neurology and neuropathic pain, especially diabetic neuropathy.

References

Abubaker SA, Alonazy AM, Abdulrahman A. Effect of Alpha-Lipoic Acid in the Treatment of Diabetic Neuropathy: A Systematic Review. Cureus 2022; 14: e25750.

Balanaser M, Carley M, Baron R, Finnerup NB, Moore RA, Rowbotham MC, Chaparro LE, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults: systematic review and meta-analysis. Pain 2023; 164: 230-251.

Benichou T, Pereira B, Mermillod M, Tauveron I, Pfabigan D, Maqdasy S, Dutheil F. Heart rate variability in type 2 diabetes mellitus: A systematic review and meta-analysis. PLoS One 2018; 13: e0195166.

Bharucha AE, Kudva YC, Prichard DO. Diabetic Gastroparesis. Endocr Rev 2019; 40: 1318-1352.

Deerochanawong C, Ferrario A. Diabetes management in Thailand: a literature review of the burden, costs, and outcomes. Global Health 2013; 9: 11

ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al, on behalf of the American Diabetes Association. 12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes-2023. Diabetes Care 2023; 46 Suppl 1: S203-S215.

England JD, Gronseth GS, Franklin G, Carter GT, Kinsella LJ, Cohen JA, et al. American Academy of Neurology. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. Neurology 2009; 72:185-192.

England JD, Gronseth GS, Franklin G, Carter GT, Kinsella LJ, Cohen JA, et al. American Academy of Neurology. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. Neurology 2009;72: 177-184.

Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, Bril V, Russell JW, Viswanathan V. Diabetic neuropathy. Nat Rev Dis Primers 2019; 5: 42.

Freeman R. Autonomic Peripheral Neuropathy. Continuum (Minneap Minn) 2020; 26: 58-71. doi: 10.1212/CON.0000000000000825.

Karaganis S, Song XJ. B vitamins as a treatment for diabetic pain and neuropathy. J Clin Pharm Ther 2021; 46: 1199-1212.

Kulkantrakorn K, Chomjit A, Sithinamsuwan P, Tharavanij T, Suwankanoknark J, Napunnaphat P. 0.075% capsaicin lotion for the treatment of painful diabetic neuropathy: A randomized, double-blind, crossover, placebo-controlled trial. J Clin Neurosci 2019; 62: 174-179. doi: 10.1016/j.jocn.2018.11.036.

Kulkantrakorn K, Lorsuwansiri C, Meesawatsom P. 0.025% capsaicin gel for the treatment of painful diabetic neuropathy: a randomized, double-blind, crossover, placebo-controlled trial. Pain Pract 2013; 13: 497-503.

Kulkantrakorn K, Lorsuwansiri C. Sensory profile and its impact on quality of life in patients with painful diabetic polyneuropathy. J Neurosci Rural Pract 2013; 4: 267-270.

Kulkantrakorn K. Capsaicin: Features usage in diabetic neuropathic pain. In Rajendram R, eds. Treatments, Mechanisms and Adverse Reactions of Anesthetics and Analgesics. Elsevier; 2022. p365-374.

Malik RA, Andag-Silva A, Dejthevaporn C, et al. Diagnosing peripheral neuropathy in South-East Asia: a focus on diabetic neuropathy. J Diabetes Investig 2020; 11: 1097-1103.

Moisset X, Bouhassira D, Avez Couturier J, Alchaar H, Conradi S, Delmotte MH, Lanteri-Minet M, Lefaucheur JP, Mick G, Piano V, Pickering G, Piquet E, Regis C, Salvat E, Attal N. Pharmacological and non-pharmacological treatments for neuropathic pain: Systematic review and French recommendations. Rev Neurol (Paris). 2020; 176: 325-352.

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2018; 3: CD012182.

Nitiyanant W, Chetthakul T, Sang-A-kad P, Therakiatkumjorn C, Kunsuikmengrai K, Yeo JP. A survey study on diabetes management and complication status in primary care setting in Thailand. J Med Assoc Thai 2007; 90: 65-71.

Nkonge KM, Nkonge DK, Nkonge TN. Screening for diabetic peripheral neuropathy in resource-limited settings. Diabetol Metab Syndr 2023; 15:55.

Price R, Smith D, Franklin G, Gronseth G, Pignone M, David WS, et al. Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary: Report of the AAN Guideline Subcommittee. Neurology 2022; 98: 31-43. doi: 10.1212/WNL.0000000000013038.

Spallone V. Update on the Impact, Diagnosis and Management of Cardiovascular Autonomic Neuropathy in Diabetes: What Is Defined, What Is New, and What Is Unmet. Diabetes Metab J 2019; 43: 3-30.

Ziegler D, Papanas N, Schnell O, Nguyen BDT, Nguyen KT, Kulkantrakorn K, Deerochanawong C. Current concepts in the management of diabetic polyneuropathy. J Diabetes Investig 2021; 4: 464-475.

Ziegler D, Tesfaye S, Spallone V, Gurieva I, Al Kaabi J, Mankovsky B, et al. Screening, diagnosis and management of diabetic sensorimotor polyneuropathy in clinical practice: International expert consensus recommendations. Diabetes Res Clin Pract 2022; 186: 109063.

"Littérature engagée" in Thailand in the Revolutionary Years from 1973 to 1976

Pornsan Watanangura

Fellow, Royal Society of Thailand, Dusit, Bangkok 10300 Thailand

Abstract

It may be a surprise that the original idea of littérature engagée in Thailand has its roots on one hand in international socialist movements in Europe, and on the other hand in the re-study of Thai literature of Thai poets in the 5th decade of the 20th century. The critical analysis of Thai literature of Chit Bhumisak in accordance with the concept of literature as "l' pure l" inquiring after the function of literature, and the 14th October Student Revolution in 1973 have marked the beginning of a new epoch in Thailand's political and social life. Students had called upon the military dictatorship to reinstate a democratic constitution. These two incidents, literary and social-politically, are decisive for the movement of littérature engagée in Thailand, which in its new character, is known under the name literature for life.

This paper aims at an understanding of how the political and literary movement in Thailand represents the first attempt to see literature as a medium for the resolution of social-political conflicts and to use it directly in the fight against injustice. The study also demonstrates the relation between the concrete political events of 14th October 1973 and *literature for life* through examples of literary fragments.

Keywords: literature for life; littérature engage/engaged literature; the 14th October-revolution; l' art pour l' art; Aksorn Sarn; Chit Bhumisak; progressive literature

Correspondence to Pornsan Watanangura, FRS(T), Royal Society of Thailand, Academy of Arts, Dusit, Bangkok 10300 Thailand. Email: wpornsan@gmail.com

1. The Student and Civilian Uprising of 1973

The student and civilian uprising of 1973 – the so-called "students' revolution" – reached its peak on 14 October 1973. Students had already often held meetings to call upon the military dictatorship, which had controlled the country since 1959, to reinstate a democratic constitution. When the military government refused all negotiations and instead arrested 13 students at Ramkamhaeng University, thousands of students and civilians gathered in a massive demonstration, which ran from Thammasart University to Democracy Monument in the centre of Bangkok and gained increasingly more support overnight. On the morning of 14 October, the police and then the military used force against the demonstrators. Many could only save themselves by entering royal grounds.

That the uprising did not become an even greater bloodbath was due on one hand to the fact that the majority of the military refused orders to fire and on the other hand to the high respect held for the king, who had asked for the demonstration to be brought to an end.

This students' revolution marked the beginning of a new epoch in Thailand's political and social life. Thai scholars speak of a new age in which democracy gains ground in Thailand, the military putsches no longer function and civilians gain a new level of awareness.

What in fact emerged in numerous explanations on social and political issues, especially with regard to civil rights, was a new political awareness particularly in the intellectual middle classes but also in the working classes and farming communities.

Demonstrations took place on a regular basis. They supported the prime minister on the abolition of American military bases in the country, but they also led to protest actions from different trade and social groups that reclaimed their rights or demanded social support. It was a time of the "blossoming of student political activities", but it also led to several punishments of communists and even to the murder of trade union leaders. Students were accused of being supported from both the right and left political groups outside the universities. As a whole, we can compare the situation in Thailand from 1973 to 1976 according to its ideological conflicts with the incidents in Germany during the Weimar Republic between 1919 and 1923 (Watanangura, 2012).

2. The Preconditions of the "littérature engagée" or "Literature fr Life" in Thailand: An Overview

At the end of the 40s of the 20th century, students and writers observed this political tension with "new eyes", especially intellectuals and poets, who began to put question the function of literature: *Literature, what for*? Looking back to the years from October 1973 to October 1976, many Thai poets and writers marked these "wonderful years" with distinction, in which "hundred flowers are in bloom". These flourishing years have been distinguished since then as the peak of the "littérature engagée" (engaged literature) or "literature of commitment" in Thailand.

A quarter of a century earlier the review of a famous and exceptionally popular book of verse from the Ayutthaya period (1350-1767) caused a shock in the literary world of Thailand. Writing in the well-respected monthly publication "Aksorn Sarn" under a pseudonym (Indrayut), the writer Asanie Ponchanthorm not only called the very popular court epic "*Lilit Phralaw*" a pornographic work, but also rejected it as a work of art. The epic is a love story between a young married King, Phralaw, and two beautiful princesses, who, at the end doomed to death. The review criticized and judged this highly valued work from the perspective and in the terminology of strict socialism.

Soon after this and in the following years from 1949 to 1952, the same publication printed numerous other articles in which Indrayut subjected traditional works of literature and many classical epics (*Khun Chang Khun Paen* and *Phra Apaimanee*, for example) to a harsh criticism from a socialist standpoint. The main objection was that such old literature is aimed solely at the worship of a defined upper class and therefore served only royalty and the nobility. Indrayut, on the other hand, as well as other literary critics later on, demanded that authors should only write for the people. With that they started an era of fierce discussion that also quickly expanded to the argument between "poesie pure" and "art for life" that originated from the West.

This new source of literary criticism together with the foundation of a writers' association in January 1950 led to a lively exchange of opinions about literature, in which for the first time arguments from a Western aesthetic also played a role. The writers' association by no means included only "progressive" authors, but also many others who were politically neutral or who recognized more traditional literature. This led to different literary proclamations that dealt intensively with questions about the nature of literature and its function in society. The introduction of the concept "littérature engagée" in Thailand is generally attributed to this literary movement in the years 1949 to 1952 (Chantimathorn, 1982; Satchapan, 1998). Although during this period entertainment literature dominated the book market and drew the largest number of readers, the increase in "progressive" literature cannot be overlooked.

This movement represents the first attempt to see literature as a medium for the resolution of social-political conflicts and to use it directly in the fight against injustice.

Since then, the Thai school of literature talks of three phases in which the "littérature engagée" developed in Thailand. *The first phase* from 1947 to 1957 is characterized by the first actions of the so-called "progressive" writers and their proclamation of "art for life" against "art for art" (l' art pour l' art). The central question was about the function of literature and the actual task of the writer. This period was distinguished in the first place in the journal "Aksorn Sarn" and continued until the demise of this journal in 1952, when Supa Sirimanon and Kularp Saipradit, together with other authors and journalists, were arrested on the 10th of November 1952 because of their political activity, the so called "Peace-uprising". This "Peace-Uprising" of 1952 resulted in many Thai authors turning to the social problems of the country and therefore, gave greater impetus to "progressive literature". This also applies to the time after the first military putsch by General Sarit Thanarat in 1957 that led to a blossoming of progressive "literature for life" in Thailand, if only for a period of a year. The second military putsch in Thailand was the major turning point, however. General Sarit abolished the constitution, dissolved parliament and governed the country with just 20 laws he set himself. Many writers and journalists were put under strict surveillance or arrested as communists. Communist actions, or actions considered as such, were forbidden and the media was heavily censored.

The political deformation and social impoverishment under the military rule, which lasted until 1973, only allowed entertainment literature and zealously eliminated any socially critical statements. However, these harsh measures also gave the impetus for a *second phase* of "littérature engagée". This phase reached its peak during the years 1973 to 1976, when the military power fled following the student revolts.

After the return of the military dictator from exile and immediately following this time an extremely bloody suppression of a student demonstration on the Thammasart campus, people soon spoke of the "death of the littérature engagée" in Thailand.

The third phase of "leftist" literature began first with the change of power from an extreme right-wing government to a largely military group following a putsch in 1977. Although political control was not exercised with as much force, many writers and books were still under prohibition. But the interest of writers and students in political engagement was also gradually waning. The third phase of the littérature engagée after 1976 is displayed more through reflections, criticism and remembrances of the brutal political persecution in the preceding phases.

3. Littérature engagée in Thailand before 1973

The fact that Thai socialism in literature deals more with the lives of farmers or the poor and their fight against the bourgeoisie, and therefore, also differs from the socialism in Europe around the end of the 1900s, illustrates the paradox of the littérature engagée in Thailand from 1947-1955:

Many short stories and novels and "songs for life," stimulated by Marxist theory, demonstrated social conflicts upcountry. As Thailand was at the time a strongly agricultural country, country life was presented as especially charming in various novels. One of the most famous novels is Saenee Saowapong's *Wanlaya's Love* (1950):

> "To conjure land for the landless and squeeze cloud bottons
> to make rain fall in times of drought…"
>
> (In the translation of Marcel Barang, 1996)

The farmers appear as "back bone, thus the mainstay for all organs, of society…",

and they claim:

> "…because they are under house registration, must report births, deaths and changes of adresse, register their boat of they have one, and even their *buffalos* must be put on the books…"
>
> (In the translation of Marcel Barang, 1996)

The literary themes did indeed include a demand for equality between the rich and poor in accordance with socialism, but it fully lacked the misery of the mass proletariat. The so-called "progressive literature" or "literature for life" far more reflected the life of the farmers on the land, and how it conformed to the real way of life in the country. Only a systematic and scholarly preoccupation with Marxist-socialist theories, such as that practiced by "Chit Bhumisak", a student in the Faculty of Arts at Chulalongkorn University, from 1995 created a stable foundation for Thai littérature engagée in later years.

In the history of the Thai littérature engagée Chit Bhumisak is revered as the most significant "thinker and poet", not only because of his literary-theoretical debate about the conception of "art". With his essays on art and literary criticism – "What is Art? Is there such as thing as 'poesie pure'?"; "What is 'l'art pour l'art"; and "What does 'art for life' mean?" – Chit carried forward the pioneering work of his predecessors during the years 1947 to 1952, particularly that of Indrayut, Banchong Banchoedsin and Saenee Saowapong. Chit Bhumisak was a student of philology and had a very good historical knowledge of the Thai language, the old classic languages of Pali, and

Sanskrit. He also knew modern Western and Asian foreign languages as well as their literature and history, so that he had a rich Euro-Asian background for his work with Marxism. This gave his literary-critical writings and his literary contributions particular credibility for many contemporary literary critics as well as those from the younger generation.

Chit Bhumisak was accused of being a communist by the military government of Field Marshall Sarit Thanarat. In May 1965, Chit went "into the woods" in order to take part in the revolutionary fight of the farmers and workers together with the Communist Party of Thailand. His sole resolution was to fight together with the "people". On 5 May 1966 he was shot dead in the woods in a province of north-eastern Thailand.

With this the previously more literary socialist battle of the Thai people gained a new realism and became for many a political reality.

4. Littérature engagée in Thailand in Revolutionary Years 1973-1976

I have given an overview of the preconditions of the littérature engagée in Thailand before 1973. We have recognized that the genesis of the littérature engagée in Thailand was not primarily the fate of the proletariat or the oppression of the military dictator. It was more the inhuman and unjust treatment of farmers and people upcountry by government officers. However, the political situation changed under the regime of General Sarit Thanarat 1958-1963, and the intensification of the dictatorship of General Thanom Kittikachon and Prapat Charusatien that prepared the path for the student uprising in October 1973.

The social-political problems which could not be solved became part of a process of literary creativity. This period was considered as "the age of chaos", also "the age in search for the meaning of life" as illustrated in a poem by Wittayakorn Chiengkul[1]:

ฉันเยาว์ ฉันเขลา ฉันทึ่ง
ฉันจึง มาหา ความหมาย
ฉันหวัง เก็บอะไร ไปมากมาย
สุดท้ายให้กระดาษฉันแผ่นเดียว

Wittayakorn Chiengkul, 1968

[1]Actually, this stanza is a part of a 7-stanza-poem *"เพลงเถื่อนแห่งสถาบัน"* (Vulgar-Song of University) by Wittayakorn Chiengkul, at the time a third-year student of Thammasat University. The poem was first published in the newspaper "Yung Thong", 27th June 2511 B.E./1968, later in a book of short stories and poem "Chan Jueng Maha Kwam Mai" *(ฉันจึงมาหาความหมาย)*, 2514 B.E./1971, and was reprinted twelve times between 2515-2542 B.E. Compare: http://dynamic.psu.ac.th/economics.psu.ac.th/mab/001_newslist_7.html

I was young, I was foolish, I was amazed,
In search of meaning, was I,
Hoping to find lots of things,
Alas, only a piece of paper, is mine.

(My translation, August 2023)

(In German) Ich war jung, ich war dumm, ich war erstaunt,
So machte ich mich auf die Suche nach dem Sinn.
Hoffe, viele Dinge zu erhalten,
Doch nur ein Blatt Papier ist zu gewinnen.

(My translation, April 1999/August 2023)

This poem, "Chan Chueng Maha Kwam Mai" (1971), puts not only the student life at universities and the meaning of the university degree in question, but it also reveals the limitation of literature in a search for the meaning of life.

Directly after the student revolution on the 14th October 1973 Naowarat Pong-paibhun described the scenes on the "The most mournful Day" (วันมหาวิปโยค), as called by King Bhumibol, in his poem *On the Day the Doves were Killed:*

A picture, after picture, becoming clearer,
A shot after shot, on human body –
Day after day, more perceptible,
midst in memory, direct, vivid – openly.

(My translation, December 2004)

(In German) Ein Bild, nach einem Bild, immer klarer,
Ein Schuß, nach einem Schuß, auf den Leib getroffen –
Ein Tag nach einem andern, wahrnehmbarer,
mitten in Erinnerung, unmittelbar, deutlich und offen.

(Meine Übersetzung, April 1999)

Another poet took a traditional cradle song with a hero from the Ayutthaya period during the war against the Burmese in 1767. The hero "Chao Kunthong" of 1973 no longer represents the hero of the past, but rather the students of the Revolution on 14th October 1973:

From Chao Khun-Thong, no trace
there, only constitution
Mother and father in a sorry state,
but proud of their son.
(My translation, August 2023)

(In German) Von Chao Khun-Thong keinen Spur,
ist da die Konstitution, nur
Mutter und Vater trauern
sind aber stolz auf ihren Sohn.
(My translation, April 1999)

The ambivalent feelings of the parents of "Chao Khun Thong" express both sides of the student uprising poetically. Some poets had given hint of the coming conflicts in Thai society, Naowarat Pongpaibhun had alluded to in his "*Mere Movement*":

…. A promise astir, of nothing evil,
But of grace, and beauty, taking shape.
There amid the murky stillness,
the beginning is begun.
Listen to the temple drums.
Observe another Holy Day.
Hear the booming of the guns
mark the people's battle-cry.
Naowarat Pongpaiboon
(Translated by Chancham Bunnag, 1998)

Another famous strophe from a young poet, Visa Kanthap, *We will Win*, became a symbol of the battle of the folk:

…เมื่อท้องฟ้าสีทองผ่องอำไพ
ประชาชนจะเป็นใหญ่ในแผ่นดิน
… when the sky gleams with golden glitter,
Over land will rule the people.
(My translation, July 2015)

(In German) …wenn der Himmel so golden glänzt
dann herrscht das Volk im Lande.
(My translation, April 1999)

So often the battles of the "free folk" were symbolized by the "red flag" and so often the Imperialism concretely with "America". In a blank verse, a poet demanded from the prime minister that he should come to the coffeeshop and take a look:

> "Whether he ever knows, what people demand. They have nothing, they desire everyday needs, they are starving. When the ruler does not react, when the society does not assist them, then they are forced to be Communists. There is no way out. "
>
> (My translation, July 2015)

During this time, the young writers wrote mainly in poetry and short stories, whereas established writers chose novel form as a means to express their literary themes for the time between 1973 and 1976. One of these renowed poets of women literature, Jiranan Pitpreecha, was honoured with her book of poem *ใบไม้ที่หายไป* (*The lost Leave*, 1989) a SEA-WRITE prize.

One of the important contributions to the prosperity of the littérature engagée in Thailand 1973-1976 was the revival of the aesthetic theory on "Literature for life", but also the book on *The Ideology of Mao Tse Tung*, published in 1974 at Thammasart University. After this publication there came more various books and essays on Marxism which were a "Tabu" before. Especially essays of "Indrayut" and Chit Bhumisak were highly esteemed. At many Universities the students organized "Poetry Reading for the Sake of Freedom", and many new magazines and newspapers with new column and book reviews for engaged literature. Young students who fought in the 14 October student revolution began to write.

In September 1974, a symposium on "The Thai Society in the Eye of Chit Bhumisak" was organized by the Society for Social Science of Thailand. Through this seminar, the work and ideas of Chit Bhumisak are widely and officially recognized among Thai intellectuals for the first time.

Chit Bhumisak's theoretical writings about art in 1955 continued to be a theoretical fund for the littérature engagée. He took his concept for these writings from Tolstoy's "What is Art? An Essay on Art," as well as from Marxist literary critics. In four essays in 1955, Chit attempted to provide a closer definition of "literature for life" that emulated Buddhist teachings. Chit's maxims for the criteria for "art for life" are:

1) Revealing the misery of life as it actually is;
2) Describing the origin of this misery;
3) Revealing the way to a life of happiness instead of misery;
4) Clear examples of the way to happiness in life, in which the "Four Noble Truths" of Buddhist teachings are:

- There is suffering - suffering is common to all.
- Cause of suffering - we are the cause of our suffering.
- End of suffering - stop doing what causes suffering.
- Path to end suffering - everyone can be enlightened.

With the maxims of "art for life" that were reclaimed from Buddhist teachings, Chit reinterpreted the core of Buddhist teachings with this analysis:

"The Buddhist philosophy corrects society in its ambitions, while the materialistic dialectics attempt to correct the structure of society, namely through revolution and not through evolution as

Buddha had already anticipated. This is the bottom line that makes the difference between the dialectic materialism and the Buddhist philosophy."

(Chit Bhumisak, in *Pii Tong-Lueang*, 1953)

In addition, Chit characterized "art for life" with three aesthetic values: beautiful, simple and clear.

5. Littérature engagée in Thailand after 1976

At its peak in 1973-76, littérature engagée in Thailand, otherwise known as "literature for life", moved to the centre of literary life not only through its poems or works of prose. In fact, at the time contributions were made by all forms of art, including fine art and music with "Songs for life", but above all by the theatre. Motivated by the political disquiet in the country, the first Brecht play was produced in Thailand (Watanangura, 2023). The "Crescent Moon" theatre group put on a production of *The Exception and the Rule*, a few months before the bloody defeat of the revolution in October 1976.

Although after a further putsch in 1977 there was a more temperate military rule, censorship remained strict, every form of public gathering was illegal and the "forbidden books" were not released. It was the time when writers used their published literary works and other means to express their memories and reflections about the brutal political events. The October putsch in 1976 was the motive for many students, intellectuals and writers to flee "into the woods" in order to continue the fight together

with the Communist Party of Thailand. Those left behind had for the most part to remain silent. Others turned to traditional themes and genres while younger authors increasingly undertook experiments with new and in part surreal methods of writing.

Everywhere, interest in politics was waning under the looser political climate. Readers also started to prefer increasingly lighter forms of entertainment literature.

Two political events - the amnesty for socialists who had gone into exile in 1979 and the break-up of the Soviet Union and international Communism in 1989 – almost caused politically engaged literature in Thailand to completely disappear.

When a special law was decreed to abolish punishments against those involved the 1976 uprising, the exiled intellectuals came back from the woods, disappointed with the outcome of their struggle. The political situation and the attitude of the population had changed to such an extent that the themes and rhetoric of politically engaged literature no longer applied to the present. The writers and former student leaders, who had made the fight between the proletariat and capitalists according to Western example one of their main topics, became skeptical and self-critical and believed the whole issue had become devalued.

In fact, the rapid economic upswing that the country experienced after a new economic plan in the early 1980s changed the circumstances of the urban population and created a luxurious way of life for many in comparison with the period before the 1970s. When the government made the ambitious attempt after 1987 to follow the example of South Korea and turn Thailand into a new industrial country, the Thai way of life increasingly resembled that of a European industrial society. Accordingly, the pursuit of private interests increasingly took the place of participation in political concerns.

When it became clear that Marxist-socialist ideology would not find wider international adoption following the collapse of socialism in the Soviet Union and the political turnaround in Eastern Europe, formal littérature engagée came to an end in Thailand. The academic revolt and the literature that it supported were based almost exclusively on international socialism. Therefore, after the political collapse of international socialism it was not possible for littérature engagée to continue to exist in Thailand as the country had no previous history of such critical political literature.

Nevertheless, this literature has left its mark with many writers and intellectuals. Many authors withdrew into a "cult of solitude" (Nagavajara, 1996). But the memory of what literature was able to stimulate in terms of thought and action in the years from 1973 to 1976 has not disappeared.

In a country where there is still injustice and where political corruption has become even worse in a parliamentary democracy, literature that deals with the condition of the people, particularly those who are disadvantaged, is not unnecessary. For without concern for the needs of human life, literature itself could become superfluous in the long run.

About the author

Pornsan Watanangura. Fellow of the Royal Society of Thailand, Academy of Arts and Emeritus Professor *Kittikhun*, Dr. phil at the Department of Western Languages, Faculty of Arts, Chulalongkorn University. President, The Thai-German Society She has been studying at the Ruprecht-Karls University Heidelberg and receiving Magister Artium M.A. (1980), Dr. phil (1985) in Applied Linguistics, New German Literature, and Music (Musikwissenschaft). Her publication in Thai, German and English comprise not only on linguistics, comparative literature and intercultural Studies, but the opening of Siam/Thailand for European culture and on the reception of Buddhism in the West. She led the translation project of the first translation of Thomas Mann's early telling stories (Erzählung) in Thailand. Prof. Dr. Pornsan was awarded the "Bundesverdienstkreuz am Band" from the Fedel Republic of Germany for her contribution in the field of German Language and Literature, Intercultural Germanistik and Thai-German cultural Relations (The Royal White Elefant Highest Rank) in the year 2018. She received the Decoration "Maha Paramaporn Chang Pueak" in 2009.

References

Chantimathorn Satien. *Literature for Life in Thailand* [In Thai]. Bangkok: Chao-Phraya Publishing; 1982.

Chitchamnong, Duangmon, Literatur Critics in Thailand 1957-1982, In: Ruengraklikit, Cholada / Satchapan, Ruenruethai / Chitchamnong, Duangmon: *Weaving Silk in Flowing Water – 200 Years Literature Critics in Thailand,* [In Thai]. Kriengkraipet, Suwanna / Chonsatitwattana, Suchitra (editors). Bangkok: Prapansarn publishing, 2nd edition, p. 218 – 291; 1998.

Nagavajara, Chetana. Brecht's Reception in Thailand. The Case of "Die Ausnahme und die Regel." In: *Comparative Literature from a Thai Perspective*, [in English]. Collected Articles 1978-1992. Bangkok: Chulalongkorn University Press; 1996. p. 95-106.

Nagavajara, Chetana, Brecht's Relevance. A Thai Perspective. In: *Comparative Literature from a Thai Perspective*, [in English]. Collected Articles 1978-1992. Bangkok: Chulalongkorn University Press; 1996. p.107-121.

Pongpaiboon, Naowarat. Mere Movement [In Thai], translated by Bunnag Chancham. In: *Thai Short Stories & Poems*. Masavisut, Nitaya and Grose, Mathew. eds. Chiangmai: Silkworm Books; 1998. p.100.

Satchapan, Ruenruethai / Rungrat, Pailin. Perspective on Literature for Life [In Thai]. In: *25 Years 14 October*. Bangkok: Chonniyom Publishing; 1998. p. 11-83.

Satchapan, Ruenruethai. Thai Short Stories 1932-1967 [In Thai]. In: *Pasa lae Nangsue*, Journal, 1998; p. 29.

Saowapong S. Wanlaya 's Love [In Thai], translated by Marcel Barang. In: *Wanlaya's Love – A Thai Novel*, The Modern Thai Classic – A collection under the Chaiyong Limthongkun Foundation. Bangkok: Express Printing; 1996.

Watananguhn, Pornsan. Opinions on the Teaching and Learning of German Language, Literature and Culture in Thailand - Theorie und Praxis, [In Thai]. In: *Intellectual Forces in Humanities, Chetana Nagavajara - Portrait of a Thai Scholar"*. Report on research project supported by Thailand Research Fund. A Bangkok: Vithithat Publishing; 1998. p. 380-426.

Watanangura, Pornsan. Bertolt Brecht: "The Good Person of Szechuan" - Anti-capitalist, Anti-buddhist? [In English]. In: *The International Journal of the Royal Society of Thailand* Volume XIII – 2021, 2023, p. 11-27. http://dynamic.psu.ac.th/economics.psu.ac.th/mab/001_newslist_7.html

Training Body and Mind for the Aged

Wichien Laohacharoensombat

Abstract

As life expectancy increases, the world's population is aging, leading to a rise in age-related illnesses. This article aims to provide guidelines and advice for individuals to manage themselves to achieve good life quality and happiness in their later years. The author, a clinical practitioner with over 45 years of experience, has observed many musculoskeletal problems, such as sarcopenia, osteoporosis, and so on, that seem to undergo the vicious cycle of deterioration. The author will discuss the importance of training the body and mind for the aged and provide evidence-based interventions to prevent or delay age-related musculoskeletal disorders so that the aged can enjoy daily physical activity and have good mental health.

Keywords: aging; musculoskeletal disorders; sarcopenia; osteoporosis; physical activity; mental health

Introduction

As life expectancy increases worldwide, many countries are experiencing a significant demographic shift towards an aging society. While living longer is desirable, the quality of life and happiness of the elderly should be considered equally important. The ability to age well and maintain good health and happiness depends on an individual's intention and effort to manage themselves towards this goal. In this article, the author provides guidelines and advice based on clinical observations and scientific knowledge gathered over 45 years of clinical practice to help the aged maintain good life quality and happiness.

Department of Orthopedic Surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University.

Correspondence to Wichien Laohacharoensombat (MD), 18 Soi Sukhumvit 34, Khlong Tan Subdistrict, Khlong Toei District Bangkok 10110, Thailand. Email: wichien.lao@mahidol.ac.th

Roots of the Matters

Many musculoskeletal problems undergo a vicious cycle of deterioration that affects the elderly population. For example, falling injuries in individuals with weak bones, such as those with osteoporosis, can lead to compression fractures in the mid-back region. This causes acute severe pain and limits physical activity, leading to weakened muscles and eventually sarcopenia. Inactivity further decreases physical activity, increases kyphosis, and completes the vicious cycle.

In another situation, habitual insults to a particular structure can lead to structural failure. The classic example is the case of an unstable back, such as spondylolisthesis, which can worsen progressively due to the habit of bending the low back during daily activities like sitting down and getting up from a chair. This motion causes stress concentration on the unstable intervertebral joint, creating gradual damage and instability that may require surgical stabilization (Wajanavisit et al, 2009; Delmonico & Beck, 2017). At this point, two types of vicious cycles can occur – one related to injury, pain, inactivity, and unstable gait, and another related to habitual non-physiologic motion, stress concentration, structural failure, inactivity, sarcopenia, and stress concentration.

Training the Body for the Aged

Physical activity is essential for maintaining muscle mass, strength, and balance, which can prevent or delay the onset of sarcopenia (Laohacharoensombat et al, 1999), osteoporosis, and other age-related musculoskeletal disorders. Resistance training, such as weightlifting, can help build muscle strength and mass, while balance training, such as yoga, can improve postural control and reduce the risk of falls. Exercise programs should be tailored to individual needs, considering their fitness level and medical conditions.

Training the Mind for the Aged

In addition to physical activity, mental health is also crucial for the elderly to maintain good life quality and happiness. Social engagement, such as participation in community activities or volunteering, can help combat loneliness and depression. Additionally, cognitive training, such as brain games and puzzles, can help maintain mental acuity and prevent cognitive decline.

Program Objective: A Program proposed from the past clinical experience

Introduction

The proposed program aims to improve posture and mobility in patients suffering from chronic pain and degenerative arthritis, thoracic kyphosis, sway back, spondylolisthesis of the low back, osteoporotic spinal fracture, fibromyalgia of the iliopsoas, and minor musculoskeletal problems. Additionally, the program intends to prevent the late development of spinal deformity and improve physical mobility in the aged. Ultimately, the program seeks to form habitual smart posture and movement, which requires concentration and awareness training of the mind. The training involves static contraction of the abdominal muscles, which is different from conventional training methods (Nejc et al, 2013; Wagner et al, 2014; Moon et al, 2015).

Theoretical Points of View

The brain operates routine daily activities in an unconscious mode, including walking, dressing, and value. The patterns of standing, walking, and sitting set by the brain are the lowest energy consumption modes, which conserve energy. Saunders et al. (1953) described the six determinants of gait based on the lowest energy consumption model. However, energy conservation can lead to sarcopenia, malposition, and joint strain in the aged. The proposed program aims to build the habit of high energy consumption modes on sitting, standing, and walking to prevent these conditions.

The Training

The program's prerequisite is the ability to perform basic meditation by observing breathing and body movement, which is helpful. In the first three months, regular daily training of 20 minutes, 12- sessions, is crucial. The trainee has the option to perform the training in either a sitting or standing posture. At the onset of the training, the trainee initiates a constant contraction of the abdomen, which is accompanied by the simultaneous contraction of other muscles in the trunk, as well as the chest muscles, and to a lesser extent, muscles in the extremities, which can be observed by the trainee. Simultaneous breathing controlled by muscles around the chest is necessary to maintain the constant abdominal contraction. This can be facilitated by concomitant motion of both shoulders and arms at the same pace of breathing in and out. Singing favourite songs with deep breathing (Draina, 2023) can help prevent boredom. Within a few months of regular training, the trainees can usually contract the abdominal muscles with normal breathing under conscious control.



Figure 1 The balance training of the body, with the constant abdominal contraction while standing on one leg and both arms elevating. (The figure is drawn by Dr. Wajana Leelapattana)

Incorporating Additional Balance Training to Improve Flexibility and Stability (Figure 1)

Introduction

Maintaining a well-balanced spinal column is crucial for optimal body motion in daily life. However, flexibility of the hips and knees also play a significant role in movement. To further enhance stability and flexibility, additional balance training exercises can be incorporated into a routine.

Objective

The objective of this program is to improve flexibility and stability in individuals who suffer from degenerative disc disease with an early state of instability. The preferred technique is a combination of passive and active stretching exercises performed without stretching the well-balanced back.

Methods

While standing on one leg, the abdomen should be kept in constant contraction and the arms should be lifted upright vertically. The opposite leg should extend backward as far as possible with the knee in full extension. The posture should be maintained for 10 seconds. For those who cannot stand on a single leg, one arm can be used to hold a stable support and only the free arm should be lifted. The training should alternate between sides and consist of 10 cycles on each side, 23- times a day.

Results

Regular practice of this technique can improve flexibility and stability, leading to a reduction in instability and pain caused by degenerative disc disease.

The further training recommended is to develop the habit of autonomously contracting the abdominal muscles when in an upright position, such as sitting, standing, and walking. This involves the practice of mindfulness in observing and maintaining the contraction. The goal of the training is to achieve constant abdominal contraction, which will then trigger contraction of the trunk and extremities whenever the trainee assumes an upright posture, leading to a higher level of energy consumption. It may take months or even years to achieve complete autonomy, but even partial achievement can bring about several beneficial effects for the body and mind, as outlined below:

- Increased body height and reduced thoracic kyphosis, resulting from abdominal contraction, which reduces lumbar lordosis and thoracic kyphosis, leading to increased body height.
- Reduced shoulder droop and neck strain in sitting posture, as abdominal contraction decreases thoracic kyphosis, activating the shoulder and neck muscles, elevating the shoulders, and reducing cervical lordosis and strain, particularly when working in an office.
- Improved gait stability and fall prevention, as abdominal contraction leads to trunk muscle contraction, reducing body swaying and increasing gait stability, thus preventing falls.
- Reduced pain and discomfort in those with early degenerative arthritis of the knees and ankles, as truncal stability decreases body swaying, ensuring that the body's centre of gravity passes through the centre of the joints in the one-legged weight-bearing phase of gait, resulting in even load distribution over the joint surface and decreased joint strain. This can prevent further development of aging arthritis of the knees.

- Enhanced meditation during both sitting and walking techniques, as the brain is occupied with controlling the abdomen, thereby eliminating the major obstacle of thinking disturbance, leading to deeper and stronger concentration, mindfulness, and better body and mind control.
- Prevention of metabolic syndrome, as constant abdominal contraction induces allied muscle contraction, leading to increased fat and carbohydrate consumption, and better control of blood sugar, lipids, and belly diameter.

It is essential to note that the above findings are based on evidence gathered from longitudinal follow-up of a limited number of patients. Further research and elucidation are necessary.

Conclusion

In summary, an alternative and efficient body and mind training program for the aged is proposed, with the aim of promoting well-being. Although the evidence of its beneficial effects is incomplete, trainees are expected to experience gradual improvement in body form and motion, as well as psychological stability and happiness during the training period.

About the author

Wichien Laohacharoensombat received his MD from Faculty of Medicine Ramathibodi Hospital, Mahidol University in 1973. After training in orthopaedics in 1977, he had been working at his alma mater until his retirement as a professor of orthopaedics in 2012. He served as head, Department of Orthopaedics in 19911999-; president, Royal College of Orthopaedic Surgeons of Thailand in 20062008-, and president of the SICOT Annual Meeting 2009 at Pattaya, Thailand.

References

Delmonico MJ, Beck DT. The Current Understanding of Sarcopenia: Emerging Tools and Interventional Possibilities. Am J Lifestyle Med 2016; 11: 167181-. doi: 10.11771559827615594343/.

Draina B. Breathing Book for Singers. [cited 2023 August 31]. https://www.mountain-peakmusic.com/breathing-book-for-singers/

Laohacharoensombat W, Wajanavisit W, Chaiyakit P. Preliminary results on the surgical treatment of disabling degenerative scoliosis. J Musculo Research 1999; 3: 285303-.

Moon JH, Hong SM, Kim CW, Shin YA. Comparison of deep and superficial abdominal muscle activity between experienced Pilates and resistance exercise instructors and controls during stabilization exercise. J Exerc Rehabil 2015; 11: 161168-. doi: 10.12965/jer.150203.

Nejc S, Loefler S, Cvecka J, Sedliak M, Kern H. Strength training in elderly people improves static balance: a randomized controlled trial. European Journal of Translational Myology 2013; 23: 85-89. doi: 10.4081/ejtm.2013.1777.

Saunders JB, Inman VT, Eberhart HD. The major determinants in normal and pathological gait. J Bone Joint Surg Am 1953; 35: 543558-.

Wagner H, Rehmes U, Kohle D, Puta C. Laughing: a demanding exercise for trunk muscles. J Mot Behav 2014; 46: 3337-. doi: 10.108000222895.2013.844091/.

Wajanavisit W, Woratanarat P, Wattanawong T, Laohacharoensombat W. Floor activities and degenerative spinal diseases. J Med Assoc Thai 2009; 92Suppl5: S8894-.

Teaching English in a VUCA World

Namthip Anantsupamongkul, Savika Varaporn

Abstract

A VUCA (volatile, uncertain, complex, ambiguous) world has brought rapid changes to our daily lives and affected education, including English language teaching. Language teachers and educators have to quickly adapt themselves to the unexpected circumstances and prepare learners for a VUCA future. This paper presents perspective on teaching English in three key areas: 1) Challenges of teaching English to Thai students in the rapidly changing era of disruption, 2) Strategies and techniques for effective English language teaching, particularly in Thai context, and 3) The significance of continuing professional development for EFL (English as a foreign language) teachers. Understanding these points will promote innovation, research, and development of new and effective teaching and learning management in the future.

Keywords: English language teaching (ELT); VUCA world; English as a foreign language (EFL) teacher

Department of Foreign Languages, Faculty of Humanities, Kasetsart University, Bangkok, Thailand

Correspondence to Namthip Anantsupamongkul (MsC), Faculty of Humanities, Kasetsart University, Bangkok, Thailand. Email: nthanikkul@gmail.com

Introduction

VUCA was recently introduced, and it has received growing attention among scholars in many disciplines. The term is an acronym that stands for volatility, uncertainty, complexity, and ambiguity (Hausberg, 2013) and is used to describe situations that are characterized by these qualities. Moreover, the term VUCA refers to the fourth industrial revolution, marked by the widespread use of computers, new technologies and the Internet in business (Nikolic & Milovanovic, 2021). The VUCA world has been continuing for a long time, but the COVID-19 pandemic has accelerated the pace of change.

It goes without saying that COVID-19 has had a devastating impact on nearly every aspect of society, from healthcare and social interactions to the economy and education. The pandemic emphasizes the VUCA nature of the world. The rapid spread of the virus and the resulting global pandemic has caused unprecedented levels of volatility and uncertainty to many sectors around the world as they had to respond to a changing situation with little precedent (Minciu et al, 2019).

In an educational setting, the pandemic has had a particularly significant impact on both teachers and students' sides. In early 2020, schools and universities had to shift to remote or online learning, either partially or fully, in order to comply with public health guidelines and prevent the spread of the pandemic. Remarkably, the emergence of the COVID-19 pandemic has left educational institutions with the challenge of preparing students who are prepared and able to adapt to VUCA situations.

In the linguistic arena, the adoption of new terms and phrases such as social distancing, self-quarantine, lockdown, or virtual learning is one of examples that highlights the changing nature of the VUCA world. Moreover, to maintain physical distancing and avoid large gatherings, traditional in-person classes have been replaced by virtual ones. This has led to an increase in the use of technology in a classroom such as video conferencing platforms, learning management systems, and self-directed asynchronous learning games. Undeniably, the classroom experience after the COVID-19 pandemic is likely to be different from the pre-pandemic one.

In this regard, questions about how to prepare an English language learner for the VUCA world arise among teachers and practitioners. This paper, then, examines such challenges and opportunities in more detail and explores strategies and techniques for effective English language teaching in a VUCA environment, especially in Thai context where English is a foreign language (EFL). Also, it discusses the importance of continuing professional development for EFL teachers in this matter.

What is VUCA?

VUCA stands for Volatility, Uncertainty, Complexity, and Ambiguity. It was originally coined by the US Army War College to describe the complex and unpredictable nature of the post-Cold War world (Hausberg, 2013). The term has since been adopted by business leaders and organizations to describe the challenging and dynamic nature of the modern business environment.

A number of scholars such as Hausberg (2013), Minciu et al (2019), Nikolic and Milovanovic (2021), and Pultoo and Oojorah (2021) defined and elaborated each quality of VUCA as follows. First, volatility refers to the speed and intensity at which change occurs. The world is full of changes that can be sudden, dramatic, and unpredictable. It is becoming difficult to understand the cause and effect of events. VUCA world demands for those who are able to adapt quickly in order to remain competitive. To survive in a VUCA environment, one needs to engage in continuous learning and access new information and technologies.

Secondly, uncertainty refers to the lack of predictability and clarity in the environment. In a VUCA world, it is difficult to use past predictions and experiences to forecast the future event. predict the future. To be successful, it is important for one to be agile, proactive, and prepared for constant change. Those who possess the ability to adapt will stand.

Complexity refers to the interconnectedness and interdependence of various elements in the environment. In this increasingly complex world, it can be challenging to understand and navigate the relationships between different variables. Choosing a single right path is becoming increasingly difficult. Therefore, VUCA is looking for those who start thinking in new ways, exploring new solutions, and innovation.

Ambiguity refers to the lack of clear definitions and interpretations in the environment. The idea that one solution can fit all situations is becoming less common and it becomes rare to find a standard routine or best practice that applies to all situations. The world is turning to be more complex, with more shades of gray than black and white. To make decisions, it requires one to take risks, be attentive, and embrace mistakes.

Exploding technological advancements, rapid demographic growth, ecological catastrophes, and geopolitical trends are a few examples of VUCA circumstances that are causing disruptions in humans' lives. The notion of VUCA has been extensively discussed in policy documents and educational contexts. The report from OECD (Organization for Economic C0-operation and Development) conference in 2018,

for instance, revealed that humans typically respond to VUCA situations in both healthy and unhealthy ways; that means they can perceive uncertainty and unpredictability as a challenge or a threat. Because of their high level of adaptability, humans frequently survive in these unpredictable environments (Laukkonen et al, 2019). For governments and policymakers, the question is how to best prepare people for a future that is becoming more unpredictable as well as how to reduce the dangers associated with quick and disruptive change.

Challenges of Teaching English to Thai Students in a VUCA World

In recent years, the role of English as a global language and the increasing demand for English language education have led to a growing demand of English speakers around the world. Moreover, the breakout of the COVID-19 pandemic in early 2020 forced an emergency remote teaching (ERT) around the world. These rapidly changing incidents have caused a number of constraints and challenges of teaching English. For example, schools have had poor online teaching infrastructure, experienced problems with teachers' competencies in the use of technology, and limited resources to all students (Carrillo & Flores, 2020). Students and teachers did not receive sufficient preparation in social-emotional competencies that were necessary for coping with such chaotic environments (Hadar et al, 2020).

In Thailand, teaching English in a VUCA world also faces a number of challenges. This article discusses the following challenges:

1) The evolving nature of language

One of the main challenges of teaching English in Thai context is the constantly evolving nature of language. New words, phrases, and expressions are constantly being introduced, and it can be difficult for teachers to keep up with these changes (Smith, 2015). In addition, new technologies and platforms are constantly emerging, which can impact the way English is used and taught (Brown, 2016). This is no exception to the Thai context.

2) The increasing diversity of Thai students, with varying levels of proficiency and cultural backgrounds

This requires teachers to be adaptable and flexible in order to meet the diverse needs of their students. Teachers are advised to use a variety of teaching methods and materials to accommodate different learning styles and needs (Williams, 2017). Some Thai students may have preconceptions or stereotypes about English or native English speakers; such preconceptions can impact their motivation and learning (Smith, 2015).

Teachers may need to address these attitudes and help students overcome any biases they may have. This involves using culturally responsive teaching techniques or promoting intercultural understanding.

3) The use of technology in classroom

Up to dates, many Thai teachers have been utilizing technology in the classroom; they prefer to use digital media technology rather than traditional methods of teaching. However, this can present both opportunities and challenges (Brown, 2016). While technology can enhance learning and make it more engaging, it can also be a source of distraction and may require additional training and resources to implement effectively (Williams, 2017). Teachers may need to find a balance between using technology to support learning and minimizing its potential negative effects.

4) Thai students' perception of the correct use of English

Many Thai students are influenced by the idea that they have to use the language like native speakers: the American and the English. They are afraid of making mistakes (e.g., using wrong grammar or mispronouncing the word) when speaking or writing. This problem does not only results in students 'low English language proficiency, but also prompts teachers to help their students overcome this obstacle. Yamalee (2018) suggested that teachers need to be open-mined and realize the diversity of the English language. English is viewed as a global language with a wide range of accents, pronunciations, vocabulary, and grammar. To meet the needs of those who speak it, the English language adapts and changes in various ways.

According to Crystal (2003), the spread of English is illustrated in Kachru (1985)'s three concentric circles (Figure 1). The inner circle represents the countries where English is the primary language. Some of those countries where English is spoken widely and used in official settings are the USA, UK, New Zealand, and Australia. The outer circle involves the nations which are former colonies of the British Empire, such as India, Malaysia, and Singapore. Lastly, the expanding circle presents the countries that English is spoken as a foreign language, such as China, Japan, Russia, and Israel.

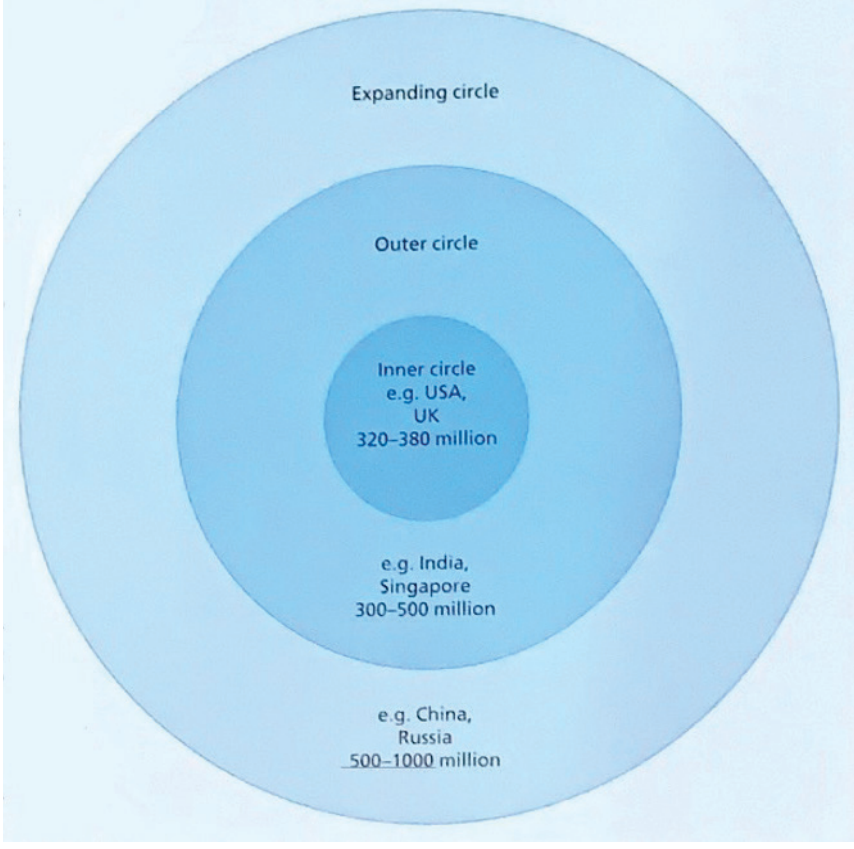


Figure 1 The spread of English language (Adopted from Crystal 2003 p.107)

As English travels around the world, students may have heard Indian English, Caribbean English, or Singlish (Singaporean English). Therefore, teachers have to adapt their teaching to be suitable for real-life communications rather than teaching students to use or memorize only the language formats of native speakers.

To sum up, English language teachers all over the world struggle substantially with VUCA situations. Being aware of the challenges in their own contexts serves as a wake-up call to boost future innovations and improvements in English language teaching and learning. This is, then, a time for teachers to focus on core learning priorities, to be intentional in how to support students, continue their own professional development, and to be flexible in their expectations (Pultoo & Oojorah, 2021).

Strategies for Teaching English as an EFL in Response to a VUCA World

Teaching English as a foreign language in a VUCA world can present unique challenges for Thai teachers. The fast-paced and unpredictable nature of the modern world can also make it difficult for Thai students to stay motivated and engaged in their language learning, and for Thai teachers to effectively plan and deliver lessons. However, with the right strategies and techniques, it is possible to create a successful and dynamic learning environment for Thai students learning English as an EFL.

One effective strategy for teaching English to Thai students in a VUCA world could be the use of a variety of teaching methods and approaches. By incorporating a range of activities and techniques, EFL teachers can keep students engaged and motivated, and help them learn more effectively (Hausberg, 2013).

Moreover, EFL teachers can emphasize soft skills such as innovation, agile leadership, and others that are essential for students to function effectively in the VUCA world. It is predicted that the need for social-emotional skills, leadership, and initiative-taking will increase, along with a greater need for cognitive, creative, and problem-solving abilities (Nikolic & Milovanovic, 2021). All of these commodities simply highlight the importance of being a lifelong learner.

Here are suggested approaches:

Collaborative learning

As the new generation has involved more in active and collaborative activities than the previous generations, it is necessary for teachers to adjust their teaching methods. Collaborative learning is an educational approach to teaching that involves groups of learners working together to solve a problem (Laal & Laal, 2012). It is a set of methods which enables students to work together to achieve a learning goal (Johnson & Johnson, 2009).

Encouraging students to work together in small groups or pairs tends to provide a number of advantages in preparing students for VUCA. Through collaboration, students could tremendously learn from their peers. Besides, they learn how to play in teams, how to raise a negotiation, or how to express an argument. This is in line with the Sociocultural Theory (SCT) by Vygotsky (1978), which argues that human learning takes place through participation in social interaction with knowledgeable others (Tuvajitt & Soontornwipast, 2017).

Collaborative learning also improves students' learning outcomes. According to Nikolic & Milovanovic (2021), learning outcomes are significantly impacted by active and collaborative learning techniques more than other techniques. In other words, when students use collaborative learning methods to work together, they can accomplish their shared objectives.

One of the collaborative and active learning environments is the "flipped" classroom. The flipped classroom model emphasizes collaborative learning that can create strong social interactions between students and teachers. Apart from strong social interactions, flipped classrooms also enhance interactive discussion and communication and problem-solving in a team with minimal guidance from teachers. In this kind of class, students participate actively in group discussions or debates after they have learned the course materials (e.g., lectures and videos) outside the classroom. Flipped classrooms enhance peer assisted learning, and help teachers understand how much their students have learned.

Since VUCA requires an individual to actively engage in the changing world, students in a flipped classroom then learn in an active and collaborative way. They have a chance to engage in activities such as problem solving, role-playing, reading, writing, and participating in discussions and debates.

Besides, it is essential that EFL teachers need to be both a facilitator and a coach at the time of collaborative learning in a flipped classroom. Teachers are suggested to use coaching techniques to help students reflect critically on what they have learned and integrate that information into their existing knowledge and beliefs.

During the students' collaboration, effective communication among students and between teachers and students promotes a positive learning environment. Good communication also fosters creative thinking and encourages students to contribute in an innovative and effective way. Therefore, the teaching style of the teachers should be tailored to the student's needs and values and should aim to help the student set objectives of their learning and of each classroom task, develop action plans, and evaluate their own progress.

Technology-assisted learning

Digital technology has become a key resource for acquiring new skills, improving business acumen, and addressing personal needs. Covid-19 has accelerated the technology-assisted learning as teaching and learning can now take place through a variety of online platforms, such as YouTube, podcasts, MOOCs, and Coursera, as well as through interactive tools like gamification and simulation. Even after the pandemic,

technology-assisted learning should remain in classrooms as part of autonomous learning as Chapelle (2001) pointed out that it can provide students with additional opportunities to practice their language skills and can help them learn at their own pace.

One major benefit of using digital technologies in EFL classrooms is that it can motivate and engage students of this generation. Teachers can facilitate the more effective teaching delivery through a wide range of technological tools (A, 2019). In a classroom, there are various game-based learning platforms and online quiz makers that teachers can use to make English learning more engaging and interactive for students. Some popular options in Thailand are Kahoot, Quizlet, Blooket, Quizzes, and Vonder Go!. These platforms allow EFL teachers to create interactive quizzes, flashcards, and games that students can participate in to test their knowledge and understanding of a lesson. They also allow for real-time feedback, tracking of student progress, and the ability to share resources with other teachers. Additionally, these platforms are extremely versatile as they can be used in both online and in-person learning environments.

Examples of popular game-based learning platforms in Thailand (Figures 2 & 3)

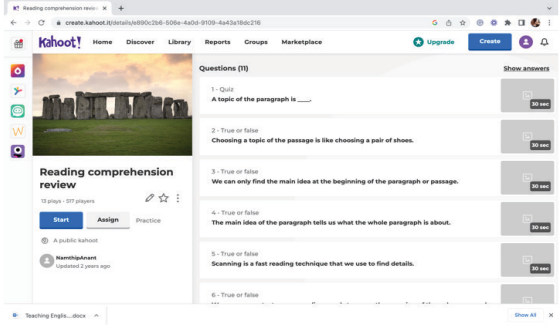


Figure 2 https://kahoot.com/

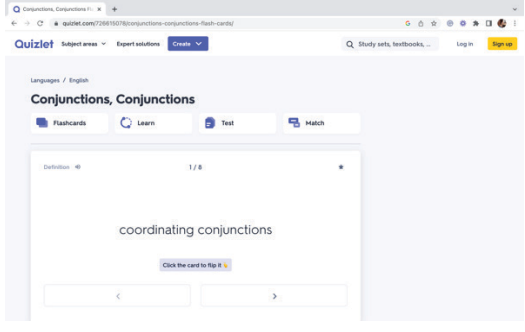


Figure 3 https://quizlet.com

However, the specific tools and approaches used would depend on the students' needs, learning style, and demographic. Different students have different needs and learning styles, and demographic factors such as age, culture, and language background can also play a role in determining the best tools and approaches for teaching and learning. For example, many games and online quiz platforms require using

smartphones and tablets or hosting synchronous activities live in a classroom is sometimes a trouble for students with poor 4G or 5G connection. To ensure that the technology-assisted approach does not disadvantage students, it is recommended that EFL teachers take into account these factors of their students and use a variety of digital tools and simulation to meet the diverse needs of their students.

Cultural immersion

Exposing students to authentic English-language materials, such as songs, movies, and news articles, can help them develop cultural knowledge and can improve their language skills through exposure to authentic language (Krashen, 1982). Language teachers can support cultural immersion through technological applications. For example, they turn an English language class into cultural settings when using multiplayer online games in class. This stimulates learning environments that allows the real world to merge with the digital world.

In addition to incorporating a variety of teaching methods and approaches, it is also important for teachers to be flexible and adaptable in their lesson planning and delivery (Moss Kanter, 2013). In a VUCA world, it is common for unexpected events or changes to occur, and teachers must be prepared to adjust their plans as needed (Hausberg, 2013). This can involve being open to feedback from students and incorporating their needs and interests into lesson plans, as well as being willing to try new teaching methods and approaches when they may be needed (Moss Kanter, 2013).

Continuing Professional Development (CPD) for Thai EFL Teachers

Continuing professional development CPD is defined as "ongoing learning programs and approaches through which teachers advance their teaching skills to ensure them to remain competent." (Speck & Knipe, 2005, cited in Tabatabaee-Yazdi et al, 2018, p.2). As a form of lifelong learning, CPD offers teachers the chance to learn new things, improve skills, and refresh their existing knowledge. By participating in CPD activities, teachers can continually 'upskill' or 'reskill', and their academic and practical qualifications will not become outdated or obsolete.

There are several reasons why CPD is important for Thai EFL teachers in a VUCA world. First, CPD can help teachers stay current with the latest research and best practices in language teaching (Hausberg, 2013). With the rapid pace of change in the modern world, it is important for teachers to be aware of new developments and techniques in their field in order to provide the best possible education for their students. CPD can help teachers learn about new teaching methods and approaches,

as well as stay updated on the latest research on language learning and acquisition (Hausberg, 2013).

Second, CPD can help teachers adapt to changes in the educational landscape (Moss Kanter, 2013). In a VUCA world, it is common for unexpected changes to occur, and teachers must be prepared to adapt to these changes in order to remain effective. CPD can provide teachers with the skills and knowledge they need to navigate new challenges and remain flexible and adaptable in their teaching.

Third, CPD can help teachers develop new skills and knowledge in areas that are relevant to their teaching (Hausberg, 2013). For example, EFL teachers may want to improve their knowledge of a particular language or culture or develop expertise in a specific teaching method or approach (Moss Kanter, 2013). CPD can provide teachers with the opportunity to pursue these interests and become more proficient in their field.

It is believed that CPD is a significant factor in teachers' creativity. Creative EFL teachers produce effective EFL instructions because there is a direct correlation between teachers' CPD and their creativity. Thus, EFL teachers can foster their creativity in these VUCA situations by familiarizing themselves with some professional development activities, such as reading journals, taking training courses, or attending educational seminars, workshops, and conferences (Mohammadifar & Tabatabaee-Yazdi, 2021). CPD can also involve sharing best teaching ideas, and viewpoints with a focus on helping teachers improve their teaching techniques.

Conclusion

We have been living in turbulent and rapidly changing environments for a long time, and the COVID-19 pandemic, an extreme case of VUCA, disrupts our lives at an increasing pace. Because of these conditions, there is a constant need for learning and creativity, and those who are well prepared for all disruptions or difficulties will benefit.

Education in this era should focus on active learning, which encourages students to complete tasks through collaborative learning. Students need to develop themselves to reach their full potential until they obtain significant 21st century skills. For language teachers, CPD is crucial as it is an ongoing process that enhances teachers' skills and competencies. Although teaching English in this era of unprecedented technological advancement, rising demand for English speakers, and limited resources presents a number of challenges, we can overcome them by being resourceful, adaptable, resilient, and persistent.

Many studies have been done on teaching English in VUCA environments outside of Thailand, but their findings might not be generalized or applied to the Thai context and educational system. Future studies are therefore needed to find out what needs and challenges of Thai EFL teachers and students are, as well as how best to prepare them for the VUCA world. We anticipate that new research will help illuminate innovative and inspiring teaching strategies and encourage effective learning.

About the authors

Namthip Anantsupamongkol is working as a lecturer at Kasetsart University, Bangkok, Thailand. Her background is in Teaching English to Speakers of Other Languages (TESOL). Her teaching and expertise are in the area of second-language reading. She is interested in action research in effective reading techniques, sociolinguistics, and metacognitive learning.

Savika Varaporn is a full-time English lecturer at the Department of Foreign Languages, Faculty of Humanities, Kasetsart University, Thailand. She received her Ph.D. degree in English Language Teaching (International Programme) from the Language Institute of Thammasat University. Her research interests include EFL reading, multimodality in ELT, and multiliteracies. She can be reached at savikav@gmail.com.

References

A AM. The Use of Technology in English Language Teaching. Frontiers in Education Technology 2019; 2:168. doi:10.22158/fet.v2n3p168.

Barrows HS and Tamblyn RM. Problem-based learning: An approach to medical education. New York: Springer; 1980.

Brown J. The impact of globalization on English language education. TESOL Journal 2016; 7: 103-121.

Carrillo C and Flores, MA. COVID-19 and teacher education: a literature review of online teaching and learning practices. European Journal of Teacher Education 2020; 43: 466-487. doi:10.1080/02619768.2020.1821184.

Chapelle CA. Computer applications in second language acquisition: Foundations for teaching, testing, and research. Cambridge, UK: Cambridge University Press; 2001.

Crystal D. The Cambridge Encyclopedia of the English Language. Cambridge University Press; 2003.

Hadar LL, Ergas O, Alpert B, Ariav T. Rethinking teacher education in a VUCA world: student teachers' social-emotional competencies during the Covid-19 crisis. European Journal of Teacher Education 2020; 43: 573-586. doi:10.1080/02619768 .2020.1807513.

Hausberg JP. VUCA - eine Herausforderung für Führung und Organisation [VUCA - a challenge for leadership and organization]. Zeitschrift für Führung und Organisation 2013; 82: 70-77.

Hmelo-Silver CE. Problem-Based Learning: What and How Do Students Learn? Educational Psychology Review 2004; 16: 235-266. doi:10.1023/b:edpr.0000034022. 16470.f3

Johnson DW and Johnson RT. An Educational Psychology Success Story: Social Interdependence Theory and Cooperative Learning. Journal of Educational researcher 2009; 38: 365-379.

Jones M. Teaching English in a VUCA world. New York: Routledge; 2018.

Krashen SD. Principles and practice in second language acquisition. Oxford: Pergamon Press; 1982.

Laal M and Laal M. Collaborative learning: What is it?. Procedia - Social and Behavioral Sciences. 2012. doi:10.1016/j.sbspro.2011.12.092.

Minciu M, Berar FA, Dima C. The Opportunities and Threats in the Context Of the V.U.C.A World," Proceedings of the International Management Conference, Faculty of Management, Academy of Economic Studies, Bucharest, Romania 2019; 13: 1142-1150.

Laukkonen R, Biddel H, Gallagher R. Preparing Humanity for Change and Intelligence: Learning to Learn as a Safeguard against Volatility, Uncertainty, Complexity and Ambiguity. Paris: OECD Publishing; 2019. p6-12.

Mohammadifar F and Tabatabaee-Yazdi M. The Power of Continuing Professional Development on EFL Teachers' Creativity. International Journal of Educational Studies. 2021; 4: 1-9. doi:10.53935/2641-533x.v4i1.50.

Moss Kanter R. (2013). The new rules of the VUCA world. Harvard Business Review 2013;91: 58-65.

Nikolic TM and Milovanovic MM. Innovative Approach to Personalized Teaching and Learning in the VUCA World. 12th International Conference on eLearning (eLearning-2021). 2021. Belgrade, Serbia.

Pultoo A and Oojorah A. Designing remote education in a VUCA world. 2020; 20: 45-52. doi:10.24297/ijct.v20i.8713.

Savery JR. Overview of Problem-based Learning: Definitions and Distinctions. Interdisciplinary Journal of Problem-based Learning 2006; 1: 9-20. doi: 10.7771/1541-5015.1002.

Smith A. Challenges and opportunities for English language teachers in the 21st century.ELT Journal 2015; 69: 441-450.

Tabatabaee-Yazdi M, Motallebzadeh K, Ashraf H, Baghaei P. Continuing Professional Development Strategies: A Model for the Iranian EFL Teachers' Success. SAGE Open 2018; 8. doi:10.1177/2158244018764234.

Tuvajitt V, Soontornwipast K. Integrating Adapted Approaches of Writing Instructions with Alternative Assessment to Improve Academic Writing Ability. Arab World English Journal (AWEJ). 2017; 9: 188-206. doi:10.24093/awej/vol9no3.13.

Williams J. Adapting to a VUCA world: Strategies for teaching English in the 21st century. English Teaching Forum 2017; 55: 14-20.

Yamalee E. The Challenge of Applying English as International Language Instructional Context of Thailand [in Thai]. Ratchaphruek Journal. 2018; 16: 19-29.

The Royal Society of Thailand: Celebration of the Upcoming Centenary

Sanya Sukpanichnant[1,2], Kesinee Chotivanich[1,3]

Abstract

The Royal Society of Thailand (RST) will reach the centenary of establishment in 2026 as the RST was originally founded as the Royal Society of Siam in the reign of King Prajadhipok (Rama VII) on 19 April 1926. Then, the name was changed to the Royal Institute of Thailand in 1934, as a government independent agency under the prime minister's supervision, consisting of three institutions: the Academy of Moral and Political Sciences, the Academy of Science, and the Academy of Arts. In 2015, the name was changed to the present one, the RST and, in 2023, there are 123 fellows and 8 honorary fellows appointed by the Royal Proclamation and 94 associate fellows. As recognized as a leader in academic excellence, the RST is responsible for the academic work of the government and a Thai language reference center. The RST provides intellectual resources for research, reference and educational services. The RST is also known for its role in the planning and regulation of the Thai language and other specific referential publications. This article provides a brief introduction and interesting issues regarding the RST, and celebration plan for the upcoming centenary of the RST in 2026.

Keywords: Royal Society of Thailand; Royal Society of Siam; Royal Institute of Thailand; Academy of Moral and Political Sciences; Academy of Science; Academy of Arts

[1] Royal Society of Thailand
[2] Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand
[3] Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

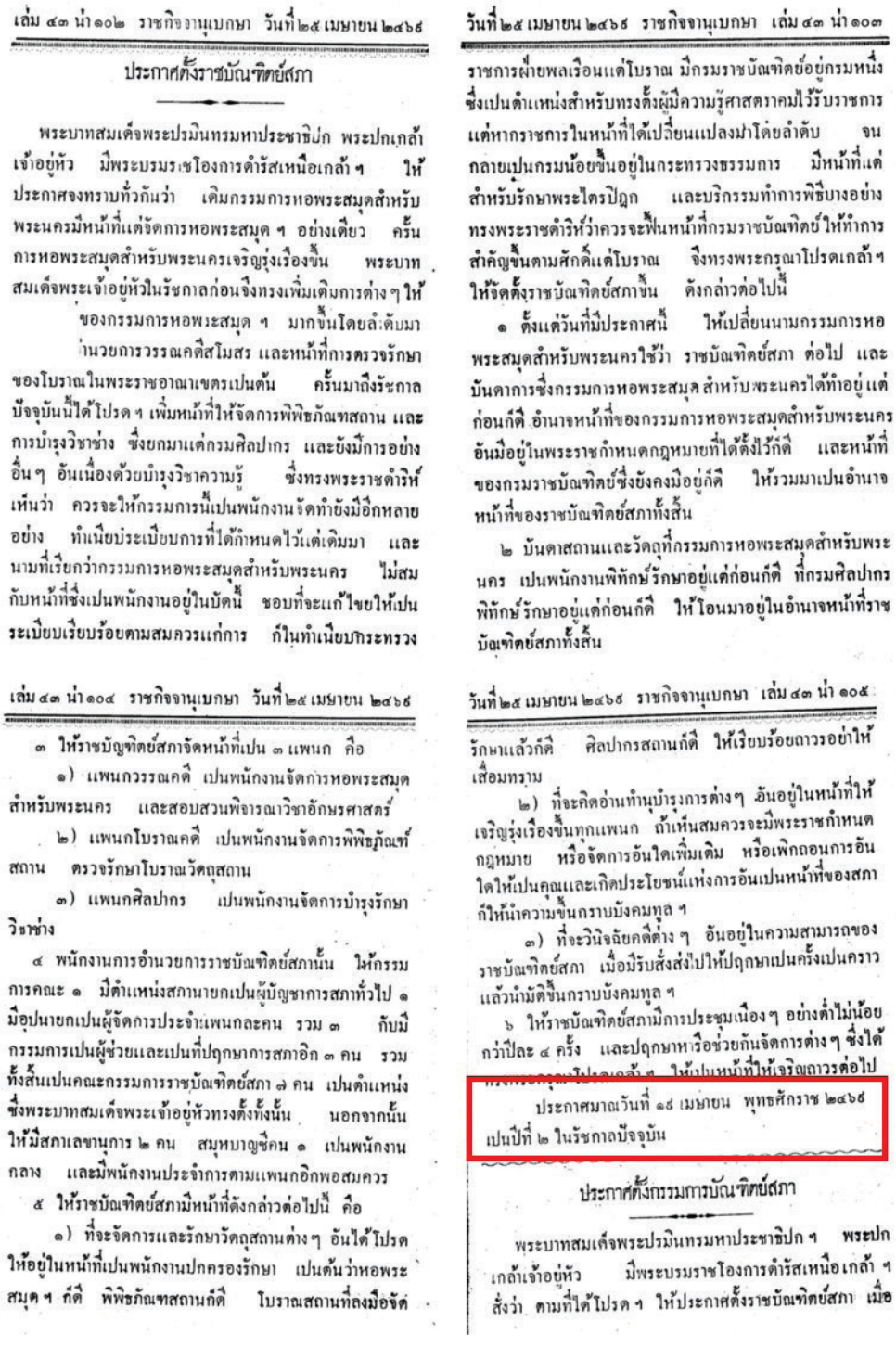
Correspondence to Sanya Sukpanichnant, MD, FRCPath (Thailand), Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
E-mail: sanya.suk@mahidol.ac.th

A Brief Introduction

The Royal Society of Thailand was originally established as the Royal Society of Siam in the reign of King Prajadhipok (Rama VII) on 19 April 1926 (Figures 1 & 2). By 2026, the society will reach the centenary – a milestone to celebrate. The Royal Society of Siam was changed to the Royal Institute of Thailand in 1934 and subsequently the Royal Society of Thailand in 2015. (The Royal Society of Thailand, 2020)



Figure 1 King Rama VII in front of the Phra Nakhon Library (the National Library), known at that time as the Vajiravudh Library located on Na Phra That Road in 1926. The illustration shows His Majesty the King standing on the carpet (center), surrounded by the King's Library Board for the Phra Nakhon Library. Prince Damrong Rajanubhab, the first president of the Royal Society of Siam, on the left hand side of His Majesty the King.



เล่ม ๔๓ น่า ๑๐๒ ราชกิจจานุเบกษา วันที่ ๒๕ เมษายน ๒๔๖๙

ประกาศตั้งราชบัณฑิตยสภา

พระบาทสมเด็จพระปรมินทรมหาประชาธิปก พระปกเกล้าเจ้าอยู่หัว มีพระบรมราชโองการดำรัสเหนือเกล้า ฯ ให้ประกาศจงทราบทั่วกันว่า เดิมกรรมการหอพระสมุดสำหรับพระนครมีหน้าที่แต่จัดการหอพระสมุด ฯ อย่างเดียว ครั้นการหอพระสมุดสำหรับพระนครเจริญรุ่งเรืองขึ้น พระบาทสมเด็จพระเจ้าอยู่หัวในรัชกาลก่อนจึงทรงเพิ่มเติมการต่าง ๆ ให้ของกรรมการหอพระสมุด ฯ มากขึ้นโดยลำดับมา ในนวยการวรรณคดีสโมสร และหน้าที่การตรวจรักษาของโบราณในพระราชอาณาเขตรเป็นต้น ครั้นมาถึงรัชกาลปัจจุบันนี้ได้โปรด ฯ เพิ่มหน้าที่ให้จัดการพิพิธภัณฑสถาน และการบำรุงวิชาช่าง ซึ่งยกมาแต่กรมศิลปากร และยังมีการอย่างอื่น ๆ อันเนื่องด้วยบำรุงวิชาความรู้ ซึ่งทรงพระราชดำริห์เห็นว่า ควรจะให้กรรมการนี้เป็นพนักงานจัดทำยังมีอีกหลายอย่าง ทำเนียบระเบียบการที่ได้กำหนดไว้แต่เดิมมา และนามที่เรียกว่ากรรมการหอพระสมุดสำหรับพระนคร ไม่สมกับหน้าที่ซึ่งเป็นพนักงานอยู่ในบัดนี้ ชอบที่จะแก้ไขให้เป็นระเบียบเรียบร้อยตามสมควรแก่การ ก็ในทำเนียบกระทรวง

วันที่ ๒๕ เมษายน ๒๔๖๙ ราชกิจจานุเบกษา เล่ม ๔๓ น่า ๑๐๓

ราชการฝ่ายพลเรือนแต่โบราณ มีกรมราชบัณฑิตย์อยู่กรมหนึ่ง ซึ่งเป็นตำแหน่งสำหรับทรงตั้งผู้มีความรู้ศาสตราคมไว้รับราชการ แต่หากราชการในหน้าที่ได้เปลี่ยนแปลงมาโดยลำดับ จนกลายเป็นกรมน้อยขึ้นอยู่ในกระทรวงธรรมการ มีหน้าที่แต่สำหรับรักษาพระไตรปิฎก และบริกรรมทำการพิธีบางอย่าง ทรงพระราชดำริห์ว่าควรจะฟื้นหน้าที่กรมราชบัณฑิตย์ให้ทำการสำคัญขึ้นตามศักดิ์แต่โบราณ จึงทรงพระกรุณาโปรดเกล้า ฯ ให้จัดตั้งราชบัณฑิตย์สภาขึ้น ดังกล่าวต่อไปนี้

๑ ตั้งแต่วันที่มีประกาศนี้ ให้เปลี่ยนนามกรรมการหอพระสมุดสำหรับพระนครใช้ว่า ราชบัณฑิตย์สภา ต่อไป และบันดาการซึ่งกรรมการหอพระสมุดสำหรับพระนครได้ทำอยู่แต่ก่อนก็ดี อำนาจหน้าที่ของกรรมการหอพระสมุดสำหรับพระนครอันมีอยู่ในพระราชกำหนดกฎหมายที่ได้ตั้งไว้ก็ดี และหน้าที่ของกรมราชบัณฑิตย์ซึ่งยังคงมีอยู่ก็ดี ให้รวมมาเป็นอำนาจหน้าที่ของราชบัณฑิตย์สภาทั้งสิ้น

๒ บันดาสถานและวัตถุที่กรรมการหอพระสมุดสำหรับพระนคร เป็นพนักงานพิทักษ์รักษาอยู่แต่ก่อนก็ดี ที่กรมศิลปากรพิทักษ์รักษาอยู่แต่ก่อนก็ดี ให้โอนมาอยู่ในอำนาจหน้าที่ราชบัณฑิตย์สภาทั้งสิ้น

เล่ม ๔๓ น่า ๑๐๔ ราชกิจจานุเบกษา วันที่ ๒๕ เมษายน ๒๔๖๙

๓ ให้ราชบัณฑิตย์สภาจัดหน้าที่เป็น ๓ แผนก คือ

๑) แผนกวรรณคดี เป็นพนักงานจัดการหอพระสมุดสำหรับพระนคร และสอบสวนพิจารณาวิชาอักษรศาสตร์

๒) แผนกโบราณคดี เป็นพนักงานจัดการพิพิธภัณฑ์สถาน ตรวจรักษาโบราณวัตถุสถาน

๓) แผนกศิลปากร เป็นพนักงานจัดการบำรุงรักษาวิชาช่าง

๔ พนักงานการอำนวยการราชบัณฑิตย์สภานั้น ให้กรรมการคณะ ๑ มีตำแหน่งสภานายกเป็นผู้บัญชาการสภาทั่วไป ๑ มีอุปนายกเป็นผู้จัดการประจำแผนกละคน รวม ๓ กับมีกรรมการเป็นผู้ช่วยและเป็นที่ปฤกษาการสภาอีก ๓ คน รวมทั้งสิ้นเป็นคณะกรรมการราชบัณฑิตย์สภา ๑ คน เป็นตำแหน่งซึ่งพระบาทสมเด็จพระเจ้าอยู่หัวทรงตั้งทั้งนั้น นอกจากนั้นให้มีสภาเลขานุการ ๒ คน สมุหบาญชีคน ๑ เป็นพนักงานกลาง และมีพนักงานประจำการตามแผนกอีกพอสมควร

๕ ให้ราชบัณฑิตย์สภามีหน้าที่ดังกล่าวต่อไปนี้ คือ

๑) ที่จะจัดการและรักษาวัตถุสถานต่าง ๆ อันได้โปรดให้อยู่ในหน้าที่เป็นพนักงานปกครองรักษา เป็นต้นว่าหอพระสมุด ฯ ก็ดี พิพิธภัณฑสถานก็ดี โบราณสถานที่ลงมือจัด

วันที่ ๒๕ เมษายน ๒๔๖๙ ราชกิจจานุเบกษา เล่ม ๔๓ น่า ๑๐๕

รักษาแล้วก็ดี ศิลปากรสถานก็ดี ให้เรียบร้อยถาวรอย่าให้เสื่อมทรุม

๒) ที่จะคิดอ่านทำนุบำรุงการต่าง ๆ อันอยู่ในหน้าที่ให้เจริญรุ่งเรืองขึ้นทุกแผนก ถ้าเห็นสมควรจะมีพระราชกำหนดกฎหมาย หรือจัดการอันใดเพิ่มเติม หรือเพิกถอนการอันใดให้เป็นคุณและเกิดประโยชน์แห่งการอันเป็นหน้าที่ของสภา ก็ให้นำความขึ้นกราบบังคมทูล ฯ

๓) ที่จะวินิจฉัยคดีต่าง ๆ อันอยู่ในความสามารถของราชบัณฑิตย์สภา เมื่อมีรับสั่งส่งไปให้ปฤกษาเป็นครั้งเป็นคราว แล้วนำมติขึ้นกราบบังคมทูล ฯ

๖ ให้ราชบัณฑิตย์สภามีการประชุมเนือง ๆ อย่างต่ำไม่น้อยกว่าปีละ ๔ ครั้ง และปฤกษาหารือช่วยกันจัดการต่าง ๆ ซึ่งได้ทรงพระกรุณาโปรดเกล้า ฯ ให้เป็นหน้าที่ให้เจริญถาวรต่อไป

ประกาศมาณวันที่ ๑๙ เมษายน พุทธศักราช ๒๔๖๙ เป็นปีที่ ๒ ในรัชกาลปัจจุบัน

ประกาศตั้งกรรมการบัณฑิตย์สภา

พระบาทสมเด็จพระปรมินทรมหาประชาธิปก ฯ พระปกเกล้าเจ้าอยู่หัว มีพระบรมราชโองการดำรัสเหนือเกล้า ฯ สั่งว่า ตามที่ได้โปรด ฯ ให้ประกาศตั้งราชบัณฑิตย์สภา เมื่อ

Figure 2 Establishment of the Royal Society of Siam in the reign of King Prajadhipok (Rama VII) on 19 April 1926 as announced in the Royal Gazette on 25 April 1926. (The Royal Gazette, 1926)

Current organization of the Royal Society of Thailand (Figure 3)

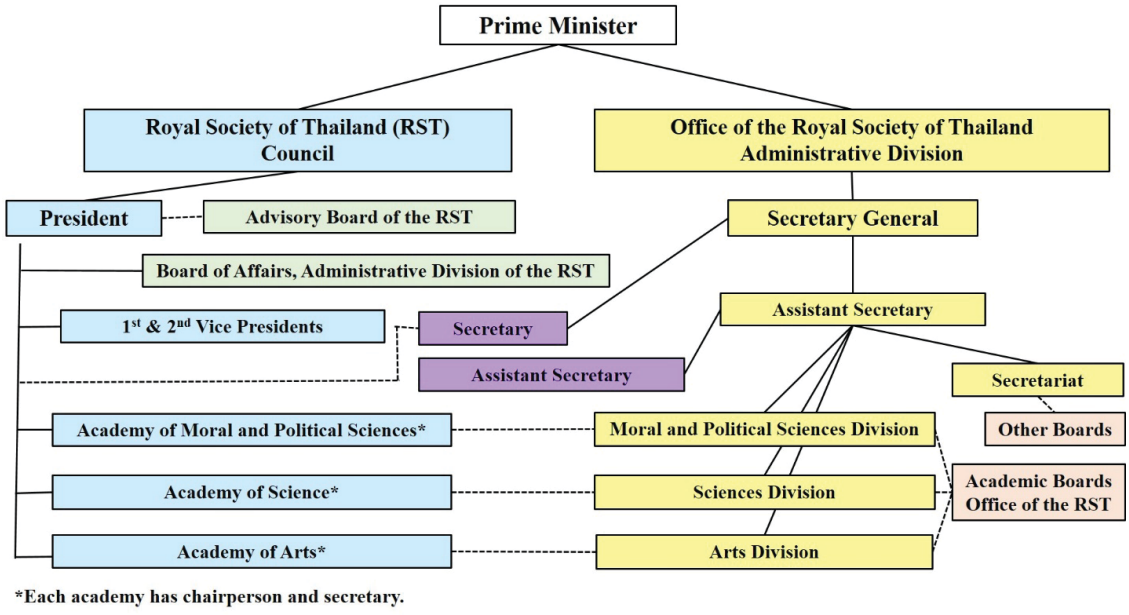


Figure 3 Organization Chart of the Royal Society of Thailand (translated from the website of the Royal Society of Thailand) (the Royal Society of Thailand, 2021)

The affairs of the Royal Society are managed by a Council and an Administrative Division. The council consists of fellows and supervises policy-making and academic affairs. The president and two-vice presidents of the council are elected every two years by the fellows. The council holds quarterly meetings in which all fellows participate in both academic and administrative activities. The Administrative Division is headed by the secretary general who is also the secretary of the council. It supports the committees whose responsibility is to carry out the academic work of the royal society. The three academic institutions hold twice-monthly meetings that provide a platform for academic presentations and adhere to specific departmental policies according to the Council of the Royal Society. (The Royal Gazette, 2015)

Mission and Activity

The Royal Society of Thailand ("Ratchabandittayasapha" in Thai) is recognized as a leader in academic excellence and consists of three institutions: the Academy of Moral and Political Sciences, the Academy of Science, and the Academy of Arts. The Royal Society of Thailand is a government independent agency under the prime minister's supervision.

The members of the Royal Society of Thailand are of three types: fellows, associate fellows, and honorary fellows. Fellows are appointed by His Majesty the King as Scholars of the King ("ratchabandit" in Thai) and are chosen from the existing associate fellows ("phakhisamachik" in Thai). Honorary fellows are also royally appointed and are chosen from renowned academic experts outside the society ("ratchabandit kittimasak" in Thai). At present (documented as of 16 December 2022), there are 123 fellows (Academy of Science 57, Academy of Moral and Political Sciences 34, and Academy of Arts 32), 94 associated fellows (Academy of Science 28, Academy of Moral and Political Sciences 37, and Academy of Arts 29, and 8 honorary fellows. (The Royal Society of Thailand, 2022)

The Royal Society is responsible for the academic work of the government and is a Thai language reference center. The society provides intellectual resources for research, reference and educational services. The society is known for its role in the planning and regulation of the Thai language and other specific referential publications. Most notably these include the official and prescriptive dictionary of the Thai language, the Royal Thai General System of Transcription, and the official system for Romanizing Thai words. The Royal Society of Thailand routinely publishes academic-specific dictionary textbooks and encyclopedias of all major disciplines and issues regular journals both in Thai and English. (The Royal Gazette, 2015; The Royal Society of Thailand, 2020)

The first three most eminent presidents of the Royal Society of Thailand (Figure 4)

The first president of the Royal Society was Prince Damrong Rajanubhab who proposed to King Prajadhipok (Rama VII) about the establishment of the Royal Society of Siam. The early tasks of the society were organizing and maintaining the National Library and the museums. Prince Damrong had contributed significantly to the modernization of the country and published numerous books and articles. He was appointed to several administrative positions during the reign of King Chulalongkorn and was the Ministry of Interior during 1892-1915. His work demonstrates his high level of dedication and genius, which is evident to the public today. He is credited as the father of Thai history, the education system, the health system, and the capital and provincial administration. In 1962, a centenary of his birth, Prince Damrong Rajanubhab became the first Thai acclaimed as a World Personage by the UNESCO (United Nations Educational, Scientific and Cultural Organization). (Damrong.org, 2023)

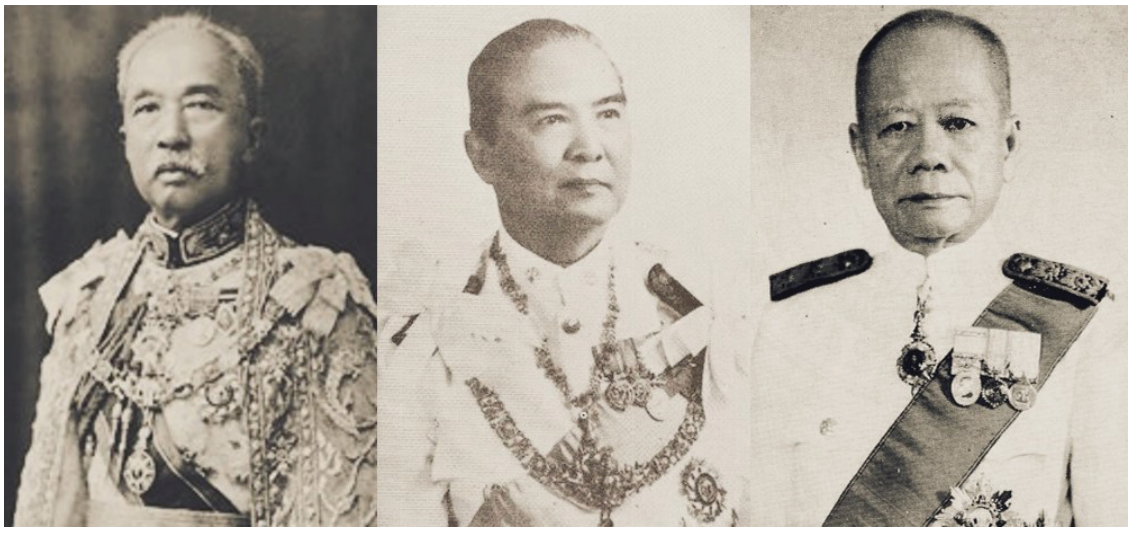


Figure 4 The first 3 presidents of the Royal Society of Thailand (from left to right): Somdet Phra Chao Borommawong Thoe Krom Phraya Damrong Rajanubhab or Prince Damrong Rajanubhab (1862-1943), Major General H.R.H. Prince Wan Waithyakon Kromamun Naradhip Bongsprabandh or Prince Wan Waithayakon (1891-1976), and Phraya Anuman Rajadhon (1888-1969).

The name of the Royal Society was changed to the Royal Institute of Thailand in 1933. HRH Prince Wan Waithayakon was the first president during 1933-1947 and 1969-1975 (acting president 1969-1973). He was a great statesman as well as an eminent literary figure. He was Deputy Prime Minister and President of the United Nations General Assembly. His talents in diplomacy and foreign affairs are recognized globally. He is famous for defining vocabulary in Thai and foreign languages. In 1989, the UNESCO declared Prince Wan Waithayakorn as a Great Scholar and Diplomat. The next president of the royal institute, Phraya Anuman Rajadhon was appointed as acting president in 1947-1969. He was a well-known academic in humanities, especially in linguistics, literature, and culture. The commemoration of the centenary of his birth was staged in 1988 by the UNESCO. (The Royal Institute of Thailand, 2014)

Celebration of the Upcoming Centenary of the Royal Society of Thailand

The Royal Society of Thailand will organize various activities to celebrate this special occasion from 2024-2026, starting with a series of academic meetings by all 3 academic institutions and the Office of the RST in every quarter as follows:Quarter 1 (January-March) by the Academy of Office of Moral and Political Sciences

Quarter 2 (April-June) by the Academy of Science

Quarter 3 (July-September) by the Office of the Royal Society of Thailand

Quarter 4 (October-December) by the Academy of Arts.

There are also other activities such as

- Construction of the statue of King Prajadhipok (RAMA VII) to be enshrined in front of the Royal Mother Luen's Residence – the new office of the Royal Society of Thailand
- Making a commemorative coin, price 20 baht
- Publishing a dictionary, the Royal Society of Thailand edition, in 2026 on the occasion of His Majesty King Vajiralongkorn's accession to the throne for 10 years and on the occasion of the Centenary of the Royal Society of Thailand establishment
- Publications from the project "The Centenary of the Royal Society of Thailand from Oral History Method"
- Publication of activities of the past and present fellows and associate fellows of the Royal Society of Thailand
- Organizing a ceremony to pay homage to the Royal Institute and senior members aged 84 years or over on the day of the establishment of the Royal Society of Thailand on April 19 annually.

About the Authors

Sanya Sukpanichnant An Associate Fellow of the Royal Society of Thailand and a Professor at Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University. He received his training in hematopathology (1990-1993) from the late Professor Dr. Robert D. Collins, who co-established the Lukes-Collins classification for malignant lymphoma in 1974. His publication focuses not only on lymphoma but also other hematologic diseases (55 and 40 articles in international and national journals, respectively).

Kesinee Chotivanich An Associate Follow of the Royal Society of Thailand and a Professor of Tropical Medicine, Mahidol University. She is the head of laboratory malaria in Mahidol-Oxford University Research Unit. Her interests are malaria pathophysiology and pharmacodynamics of antimalarial drugs. She provides clinical-related laboratory training and works with malaria research teams on international multi-center clinical trials, especially for tracking artemisinin resistance.

References

Damrong.org. Prince Damrong Rajanubhab. 2023. [in Thai]. [cited 2023 September 9]. http://www.damrong.org/?p=3834.

The Royal Gazette. Establishment of the Royal Society of Siam. 1926. [in Thai]. [cited 2023 September 9]. https://ratchakitcha.soc.go.th/documents/1075516.pdf. https://ratchakitcha.soc.go.th/documents/1075517.pdf.

The Royal Gazette. Establishment of the Royal Society of Thailand. 2015. [in Thai]. [cited 2023 September 9]. https://ratchakitcha.soc.go.th/documents/2033425.pdf.

The Royal Institute of Thailand. The 80th anniversary of the Royal Institute of Thailand. 2014. [in Thai]. [cited 2023 September 9]. https://www.orst.go.th/pdfjs/web/viewer.html?file=/FILEROOM/CABROYINWEB/DRAWER004/GENERAL/DATA0004/00004210.PDF.

The Royal Society of Thailand. The International Journal of the Royal Society of Thailand 2018: X;123-127. https://www.orst.go.th/pdfjs/web/viewer.html?file=/FILEROOM/CABROYINWEB/DRAWER004/GENERAL/DATA0004/00004926.PDF.

The Royal Society of Thailand. History of the Royal Society of Thailand. 2020. [in Thai]. [cited 2023 September 8]. https://www.orst.go.th/iwfm_list.asp?p=ABOUT-HISTORY-ORS.

The Royal Society of Thailand. Organization chart of the Royal Society of Thailand 2021. [in Thai]. [cited 2023 September 8]. https://www.orst.go.th/iwfm_list.asp?p=ABOUT-ORGCHART&s=0.

The Royal Society of Thailand. Fellows, Associate Fellows, and Honorary Fellows of the Royal Society of Thailand 2022. [in Thai]. [cited 2023 September 8]. https://www.orst.go.th/iwfm_list.asp?p=ABOUT-RBD&s=1.

Submission Guide for Authors

The International Journal of the Royal Society of Thailand (IJRSTh) is a peer-reviewed journal, and all rights are reserved.

IJRSTh publishes original articles of all academic disciplines (e.g. science, law, history, arts, music) including:

- Research articles
- Brief reports/communication
- Review articles
- Book reviews
- Perspective commentaries
- Letters to the editor
- Other related academic articles

Style and Policy Guide

- Cover Letter and Signatures
- Format Requirements
- Article Structure
- References
- Tables, Figures, and Illustrations
- Abbreviations

Cover Letter and Signatures

All manuscripts should be accompanied by a cover letter with the following information:

- Title of the paper
- First and last names of all contributing authors
- A statement affirming that the material is original, it has not been submitted for publication elsewhere, and it will remain exclusive to IJRSTh during its consideration
- Signatures of all contributing authors
- Title and present position of each author

Format Requirements

- Papers submitted must follow the designated article structure.
- The main text must be in Times New Roman, 12-point type, and 1.5 –spaced, with a 1-inch margin on all sides. This formatting applies to table and figure legends, tabular material, and references.
- The paper should not exceed 20 pages, including illustrations and the bibliography.
- The footnote must be in Times New Roman, 10-point type, single–spaced.
- All pages must be numbered consecutively, starting with the title page.
- The paper must be submitted to the Editorial Board in an electronic text (e.g., doc format).
- Either English or American spelling can be used, but should be consistent with the entire article.

Article Structure

Each article should contain the following components:

- Title
- Short title for page headings (not more than 5 words)
- Authors and their affiliations, with the full contact address of the corresponding author
- Main text: Introduction, Materials and Methods, Results, and Conclusion
- About the authors: information about each author (50-70 words)
- References (of all articles cited in the text) or bibliography
- Table and figure captions (sequentially numbered in accordance with their appearance in the text)
- Abbreviations given in full at the first mention

Abstract

The abstract must be provided in English. The abstract should be concise and informative, containing not more than 300 words. It should not only indicate the overall scope of the article but also state the main results and conclusions. There should be 5-10 keywords at the end of the abstract.

Ethical Guidelines

For experimental investigation papers, the Materials and Methods section should include the following information:

1) Informed consent from all participants and parents or legal guardians of minors, including the name of the appropriate institutional review board that approved the project
2) The maintenance and care of experimental animals complying with the Thai National Institute of Health Guidelines for the humane use of laboratory animals, or those specified by the equivalent authority in the respective country
3) Approval from the relevant ethical committee

References/Bibliography

References within the text are listed by giving the authors' last names, commas, the year of publication and pages. In the references section at the end of the article, list all authors' last names in alphabetical order. Authors are indicated by their last names, followed by a space and their initials of their first names. Individual authors' names are separated by commas.

References in the text:

References in the text should include the author's last name and the publication year. If there are two authors, the last names of both authors should be included. In the case of three authors or more, only the first author's last name is followed by "et al." The following examples are to illustrate what in-text citations look like: (Issaragrisil, 2000) for a single author, (Pukrittayakamee & White, 2018) for two authors, and (Issaragrisil et al, 2002) for three or more authors. Multiple citations of the same piece of information are separated by " ; " such as (Gordon et al, 2014; Vanker et al, 2017; Adaji et al, 2019).

References at the end of the article:

References listed at the end of the articles should include only the works mentioned in the article, and they should be arranged alphabetically based on the last names of the first authors.

Article citations:

Last name(s)/initial(s) of the author(s)'s first name(s)./full title of the article./name of the journal as abbreviated/year; volume number: first-last page numbers./doi:

(*A space in each reference is represented by /.)

All authors must be listed but if more than 20 list only the first 6 to be followed by et al.

Consult Index Medicus for accepted journal abbreviations; if a journal is not listed, spell out the journal title in full.

White NJ, Pukrittayakamee S, Phyo AP, Rueangweerayut R, Nosten F, Jittamala P, et al. Spiroindolone KAE609 for falciparum and vivax malaria. N Engl J Med 2014; 371: 403-410.

Shetty AC, Jacob CG, Huang F, Li Y, Agrawal S, Saunders DL, et al. Tracking Resistance to Artemisinin Collaboration (TRAC). Genomic structure and diversity of Plasmodium falciparum in Southeast Asia reveal recent parasite migration patterns. Nat Commun 2019; 10:2665. doi:10.1038/s41467-019-10121-3.

Online citations:

World Health Organization. Outbreak encephalitis 2005: Cases of Japanese encephalitis in Gorakhpur, Uttar Pradesh, India. 2005 Oct 21 [cited 2006 Jul 11]. http://w3.whosea.org/en/Section1226/Section2073

RWJF. The Five Deadliest Outbreaks and Pandemics in History. 2013 Dec 16 [cited 2016 Jun 11]. https://www.rwjf.org/en/blog/2013/12/the five deadliesto.html

Ben Amor Y, Nemser B, Sing A, Sankin A, Schluger N. Underreported threat of multidrug-resistant tuberculosis in Africa. Emerg Infect Dis. 2008 Sep [date cited]. http://www.cdc.gov/EID/content/14/9/1345.htm

ProMed Citations:

Lipkin I. West Nile–like virus: PCR primers and protocols. ProMed. 1999 Oct 13. http://www.promedmail.org, archive no. 19991013.1826.

Books/ Book chapters:

name(s) and initial(s) of author(s). full title. edition. place of publication: publisher; year. page number.

Olive EA. Lymphatic Filariasis Infection and Disease. London: Academic Press; 1995.

Hofstede G and Hofstede GJ. Cultures and Organizations: Software of the Mind. Revised and expanded. 2nd ed. New York: The McGraw-Hill; 2005.

Cochrane J. Great Plagues. In: An Illustration History of Medicine. Cochrane J. ed. London: Tiger Book International PLC; 1996. p80-82.

Non-English articles:

Use the same format as above but translate to English and specify the original language in brackets after the title. The translation of non-English article is optional for the online citation.

Pukrittayakamee S and Hanboonkunupakarn B. Rat bite fever [in Thai]. The Journal of the Royal Institute of Thailand 2012; 37(4): 52-57.

Anupongphongphat N and Chokevivat V. Roy Time: The Path of Health History [in Thai]. In: Komatra Chuengsatiansup ed. Bangkok: Suksala Books. 2013.

Hfocus. กำเนิดและสิ้นสุดโรคระบาดร้ายแรงในอดีต ตอนที่ 1 กาฬโรค. 2014 Aug 15 [cited 2020 March 6]. https://www.hfocus.org/content/2014/08/7906.

Hfocus. The origin and end of severe epidemics in the past. Chapter 1 Plague. 2014 Aug 15 [cited 2020 March 6]. https://www.hfocus.org/content/2014/08/7906.

Tables, Figures and Illustrations

- Tables should be numbered and referred to in the text by their numbers. Table captions should be brief, with descriptions of experimental detail(s) given directly beneath, in parentheses. Column headings, the units of measurement, and any numerical factors should be placed at the head of each column. Units should be contained within parentheses – for example, distance (cm).
- Figures and images should clarify or shorten the text. They must be sent in an electronic format that is acceptable for reproduction and is of high quality, such as .tif and .jpg. **Figures, illustrations, and online images from other sources must be fully acknowledged in the caption, and written permission sought before use. Any violation of copyright rules is the author's own.**

Address for Submission

The Editor of The International Journal of the Royal Society of Thailand,
The Royal Society, Sanam Suea Pa, Dusit, Bangkok 10300, Thailand.
Tel: 0 2356 0466-70, ext. 2045, 4016, 5022
e-mail : Yolada Yaiprayoon <ijrsth@gmail.com>