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IMR NEWSLETTER

INSTITUTE FOR MEDICAL RESEARCH MALAYSIA

Institute for Medical Research

ISSUE: 4/2019

VISIT TO IMR BY HIS EXCELLENCY H.E. DR. TAKESHI KASAI,

PG - 04

WORLD HEALTH ORGANIZATION WHO REGIONAL DIRECTOR FOR THE WESTERN PACIFIC

Kick off of *Wolbachia* infected mosquitoes program by Minister of Health

PG - 06

NMCRC - InTEX Gold Medallist for "On site Iodine Detector OSID Kit"

PG - 08

"Love Research, Love IMR, Love Nation"

IMR Director's Message

> "...I am very proud to be part of this premier Biomedical Research Institute which has contributed significantly towards research excellence in MOH. In this issue of the Newsletter, we wish to highlight some of the exciting events that have taken place at IMR."

It is an honour to be given this opportunity to helm IMR upon the retirement of Dr. Zubaidah Zakaria. Our best wishes for her retirement and we thank her for the exemplary services at this institute. As the Director, I am very proud to be part of this premier Biomedical Research Institute which has contributed significantly towards research excellence in MOH. In this issue of the Newsletter, we wish to highlight some of the exciting events that have taken place at IMR.

We were privileged to have H.E. Dr. Takeshi Kasai, the WHO Regional Director for the Western Pacific to visit IMR on 10 July 2019. Dr. Takeshi was very impressed with the facilities and research conducted at IMR, especially with the *Wolbachia* research project. The release of *Wolbachia*-infected mosquitoes is an innovative approach in the control of mosquito-borne diseases mainly Dengue. This initiative was launched by The Minister of Health, YB Datuk Seri Dr. Dzulkefly Ahmad on 7 July 2019.

Heartiest congratulations to the Nutrition, Metabolism and Cardiovascular Research Centre (NMCRC) for winning the Gold Medal at the InTEX Innovation Technology for their "On-Site Iodine Detector Kit" invention on 24-25 July 2019. We are also proud to announce the establishment of the Biobank Unit which functions as a repository of cancer biospecimens for impactful medical research.

This Newsletter is the means for us to reach our readers on the developments in IMR and I congratulate all contributors and the editorial team for their dedication that resulted in the publication of this issue.

Dr. Hj Tahir Aris
Director
Institute for Medical Research (IMR)

31 December 2019

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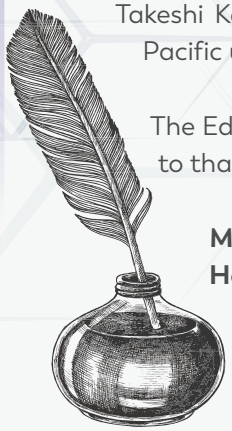
CO EDITOR-IN-CHIEF'S *Message*

Salam,

In this issue of July to December 2019, IMR welcomes the new Director of IMR, Dr. Hj. Tahir Aris who has taken over from Dr. Zubaidah Zakaria. We thank Dr. Zubaidah for her leadership and contribution. Some notable updates are the *Wolbachia* project which gave IMR some limelight in the eyes of Ministry, the public as well as the World Health Organization. This translational research project received an applause by H.E. Dr. Takeshi Kasai, WHO Regional Director for the Western Pacific upon his visit to IMR.

The Editorial team would like to take this opportunity to thank all the contributors of this Newsletter.

Mr. Mohd. Zainuldin Taib,
Head of Biomedical Museum Unit, SRC



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VISIT BY H.E. DR. TAKESHI KASAI, WORLD HEALTH ORGANIZATION (WHO) REGIONAL DIRECTOR FOR THE WESTERN PACIFIC

>> 10 JULY 2019

We were honoured to have H.E. Dr. Takeshi Kasai, the WHO Regional Director for the Western Pacific visit IMR. Y.Bhg. Datuk Dr. Christopher Lee, Deputy Director General of Health (Research and Technical Support) welcomed His Excellency to the IMR Biomedical Museum. His arrival was graced by the 'SeniTari' dancers of IMR which followed by a visit to the *Wolbachia* Laboratory where he learnt about the innovative research on dengue control using *Wolbachia*-infected mosquitoes. Dr. Takeshi was impressed with the work at IMR and wishes to forge a long-term research relationship with WHO to contribute towards the healthcare in Malaysia.

Dr. Takeshi Kasai being greeted by YBhg. Datuk Dr. Christopher Lee, TKPK (P&ST)

'SeniTari' dancers of IMR gracing H.E. Dr. Takeshi Kasai

Signing of the commemorative plaque by Dr. Takeshi Kasai at the Biomedical Museum

VISIT BY H.E. DR. TAKESHI KASAI, WORLD HEALTH ORGANIZATION (WHO) REGIONAL DIRECTOR FOR THE WESTERN PACIFIC

>> 10 JULY 2019

Dr. Takeshi introducing his hand into a cage containing male mosquitoes to experience that male mosquitoes do not bite.

Dr. Nazni, our entomologist, explaining the findings of the *Wolbachia* based control of mosquito-borne virus transmission research.

Dr. Zubaidah presenting a summary of research produced by IMR

Dr. Takeshi giving IMR thumbs-up for its good work.

KICK-OFF OF THE RELEASE *WOLBACHIA*-INFESTED AEDES MOSQUITOES BY HEALTH MINISTER YB DATUK SERI DR. DZULKEFLY AHMAD

>> 7 JULY 2019

Health Minister, YB Datuk Seri Dr. Dzulkefly Ahmad officiated the release of Wolbachia-infected mosquitoes as the means of controlling mosquito-borne diseases mainly Dengue. Also present was YB. Mdm. Teresa Kok, Parliamentary member of Seputeh. A pilot project in 2017 carried out in eight areas in Selangor showed reductions of between 50% and 80% of dengue cases in each location.

This was held at the Apartment Sri Rakyat, Jalan 14/155C, Bukit Jalil in Kuala Lumpur to educate and engage the community in this initiative. The Health Department of Wilayah Persekutuan Kuala Lumpur briefed the community and distributed education materials.

Subsequently, the release of the Wolbachia-infested mosquito eggs is being implemented in 11 localities with the support of the State Health Districts. The Wolbachia project is an example of research conducted by IMR which is being translated into a public health policy.

IMR and State Health District Office engaging the public in the release of the mosquitoes

YB Datuk Seri Dr. Dzulkefly Ahmad, Health Minister, and YB Mdm. Teresa Kok, Parliamentary member of Seputeh viewing the educational materials with the community

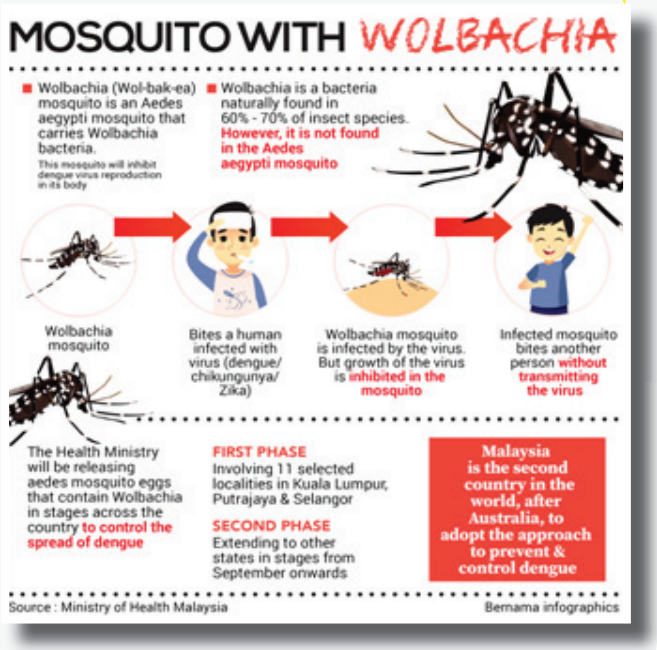
RELEASE OF *WOLBACHIA*-INFESTED AEDES MOSQUITOES ON TV3 MALAYSIA HARI INI (MHI)

>> 9 JULY 2019

Dr. Nazni Wasi Ahmad from Medical Entomology, IMR and Dr. Norhayati Mokhtar from the Vector-Borne Disease Control Sector of Ministry of Health spoke to the public through the TV3 Malaysia Hari Ini (NHI) on the release of *Wolbachia*-infected Aedes mosquitoes as a measure to control mosquito-borne diseases mainly Dengue.

The success, the mechanism and the safety of of this strategy was explained. Public was urged to be engaged and support this initiative.

Release container that contain *Wolbachia*-infected mosquito eggs and Ovitrap container used to monitor the presence of the *Wolbachia*-infested mosquitoes



YB Datuk Seri Dr. Dzulkefly Ahmad, Health Minister, and YB Mdm. Teresa Kok, Parliamentary member of Seputeh with the containers

"ON-SITE IODINE DETECTOR (OSID) KIT" GOLD MEDALIST AT INTEX INNOVATION TECHNOLOGY EXPO

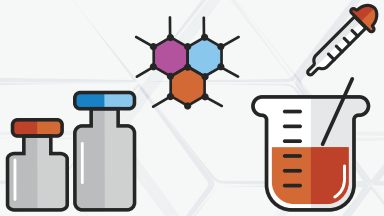
>> 24 – 25 JULY 2019

The Nutrition, Metabolism and Cardiovascular Research Centre (NMCRC) achieved Gold Award at the InTEX in Kuching Sarawak for the development of "On-site Iodine Detector (OSID) Kit". The level of total iodine in the commercial iodized salt in the port of entrance, supermarkets, and even in the rural area has to be monitored to ensure the compliance with the range specified in the Malaysian Food Act 1983. The existing method is laborious, costly and requires the expertise of a well-trained operator. Hence this OSID kit, using an electrochemical technique with screen-printed carbon electrode, was developed as a user-friendly and cost effective method for the fast and easy quantification of total iodine.

The outer and inner side of the On-site Iodine Detector (OSID) kit

The Gold Award and Certification of Achievement

The kit contains a mini spatula, small pestle and mortar, small tubes, sample tubes with specific solution, waste boxes and waste bags, alcohol swabs, Pasteur pipet, solutions for Iodine Rapid Test kit, solution for anti-oxidant, and a detector device with electrodes. The complete instruction and procedure is also provided in the kit. One complete kit can accommodate up to 48 samples. The complete analysis time for one sample using OSID kit is less than 10 minutes.



NATIONAL BIOBANK CONSORTIUM INITIATIVE

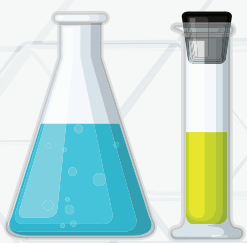
>> 11 SEPTEMBER 2019

The IMR Biobank Unit formed in April 2019 following a discussion held on the 27th of March 2019 with the Director-General of Health Malaysia, Datuk Dr Noor Hisham Abdullah and Director of IMR, Dato' Dr Fadzilah Kamaludin. The main function of the Biobank Unit is to collect, annotate, process, store and distribute quality biospecimens & associated clinical data in an ethical manner for impactful & quality medical research within the Ministry of Health (MOH). The Biobank Unit's focus will be on Cancers of National Interest. The unit also provides consultancy services for projects that require biospecimen collection as part of their research protocol.

The Biobank of IMR

In a recent meeting held on the 11th of September 2019, Dr. Zubaidah Zakaria, the Chairperson of Malaysian National Biobank Consortium Taskforce and acting Director of IMR updated the Director General of MOH on the direction and activities of the Malaysian National Biobank Consortium Initiative spearheaded by the Biobank Unit of IMR. The meeting was also attended by representatives from Malaysian Public Universities, Pathology Services MOH, Institute for Medical Research MOH and Health Informatics Centre MOH. The DG was very supportive and emphasised the need to engage public and private stakeholders to establish a sustainable, consolidated National Biobank Consortium.

The National Biobank Consortiuum Taskforce with Datuk Dr. Noor Hisham Abdullah, DG of Miistry of Health Malaysia



RETIREMENT OF DR. ZUBAIDAH ZAKARIA & HAND-OVER OF DUTIES TO DR. TAHIR ARIS AS DIRECTOR OF IMR

>> 18 SEPTEMBER 2019

Dr. Zubaidah Zakaria, acting Director of IMR retired on the 18th September 2019 upon 28 years of service in IMR and 35 years in the Ministry of Health. She handed over her duties to Dr. Hj. Tahir Aris, who took over effective from 20th September 2019..

Dr. Zubaidah handing over duties to Dr. Hj. Tahir Aris

A farewell lunch with Heads of Centres of IMR

Last "punch out" by Dr. Zubaidah

Dr Zubaidah bidding farewell

POSTER WINNERS AT PATHOLOGY CONFERENCES

Annual Scientific Meeting of College of Pathologist, Riverside Majestic Hotel, Sarawak - 26-28 June 2019

POSTER presenter :

1.) **Best top 3 for original article category –**

Dr. Yuslina Mat Yusoff
(Haematopathologist),
Haematology Unit, Cancer Research Centre (CaRC)
Title : *Genomic Landscape of Bcr-abl Kinase Domain Mutation in CML Patients with Imatibib Resistance*

2.) **Second runner up for case report category –**

Dr. Ernie Neiza (Haematopathologist),
Haematology Unit, CaRC
Title : *A Rare Hemoglobin Variant, Hemoglobin Singapore, [α141], Arg-> Pro), in a Malay Family*

3) **Third runner up for case report category –**
Dr. Alifah Nadia (Medical Officer),
Haematology Unit, CaRC
Title : *Novel Translocation t(7;11)(p22;q14) with t(8,21)(q22;q22) in A cute Myeloid Leukemia: Its Clinical Significance and Benefits of conventional Cytogenetics Over Molecular Identification*

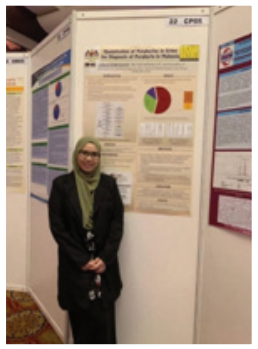
National Pathology Conference, KSL Hotel and Resort, Johor Bahru - >> 26-27 August 2019

POSTER presenter :

1.) **First prize-**
Dr. Mohan Rao (Medical Officer),
Bacteriology Unit, Infectious Disease Research Centre (IDRC)
Title : *Molecular Characterization of carbapenam-resistant Acinetobacter baumanii isolates from Malaysian Hospitals*

2) **Second prize -**
Dr Sofwatul Mukhtarah Nasohah (Medical Officer), Biochemistry Unit,
Special Diagnostic Centre (SRC)
Title : *Quantitation of Porphyrins in Urine for Diagnosis of Porphyria in Malaysia*

3) **Third prize –**
Pn Rosnani Mohamed (Research Officer)
Inborn-Error Metabolism (IEM) and Genetic Unit, Nutrition, Metabolism and Cardiovascular Research Centre (NMCRC)
Title : *Fibroblast Growth Factor 21 as Potential Biomarker for Patients with High-Risk of Mitochondrial Disorders'*



FIRST PRIZE FOR POSTER
DR. MOHAN RAO, BACTERIOLOGY UNIT, IDRC.

Molecular Characterization of carbapenem-resistant *Acinetobacter baumannii* isolates from Malaysian Hospitals, (2011-2016)

Mohan Rao[1],Fairuz Abdul Rashid[1], Norazah, Ahmad[1].
[1]*Bacteriology Unit, Infectious Disease Research Center, Institute for Medical Research, 50588 Jalan Pahang, Kuala Lumpur.*

Introduction

Acinetobacter baumannii is an opportunistic nosocomial pathogen poses significant threat to public health and associated with high mortality[1,2]. It is predominantly found among health care-associated organism with potential of substantial antibiotic resistance, grouped as ESKAPE. Carbapenem resistant A.baumannii (Cr-Ab) was identified as critical organism based on global priority pathogen list due to its unpredictable antibiotics susceptibility patterns[3,4]. Cr-Ab has become a major concern among health care facilities due to its rising prevalence along with MRSA and ESBL producing pathogens. According to National Surveillance Antibiotic Resistance database, Cr-Ab prevalence in Malaysia ranges from 50-60% and remained static since year 2008 upto 2016[5]. However, several studies from different hospitals in Malaysia showed Cr-Ab prevalence higher than the national surveillance. Carbapenem resistance in *A.baummanii* can be mediated by various mechanisms. Carbapenemase enzyme production is frequently encountered mechanism in Cr-Ab, which can be either intrinsic or extrinsic(acquired) of origin that confers unpredictable susceptibility to beta-lactams[6].

Objective

To analyze the molecular characteristics of 13 *A.baumannii* isolates obtained from hospitalized patients in Malaysia with underlying carbapenem resistance phenotype.

Methodology

13 Carbapenem resistant *A.baumannii* isolates were selected from National CRE programme of year 2011-2016.

↓

A.Baumannii identification confirmed by API 20E and Antibiotic sensitivity testing determined via E-test for Ertapenem, Imipenem and Meropenem.

↓

Bacterial DNA extraction and Whole genome sequencing

↓

De novo Assembly & Data Analysis

Results

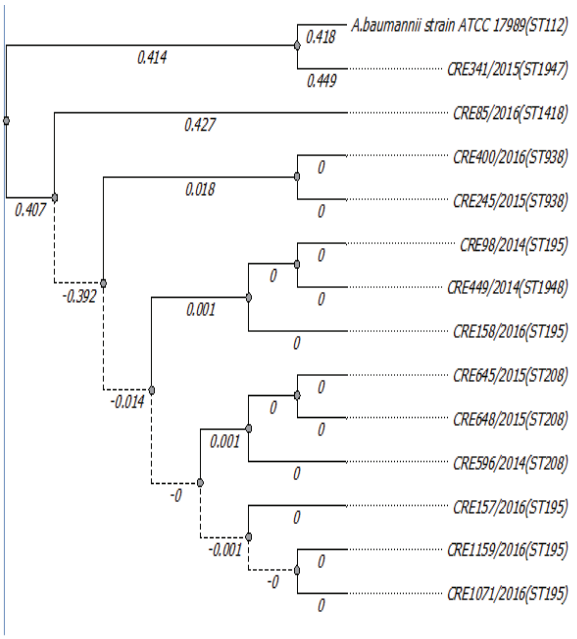


Figure 1: SNP Phylogenetic tree of *A.baumannii* isolates by year 2011-2016.

Isolate	Specimen type	Hospital	State	ST	Genes
CRE 1071/2016	Pus	HRPZ	Kelantan	195	3786
CRE 1159/2016	Urine	Shah Alam	Selangor	195	3759
CRE 157/2016	Urine	HRPB	Perak	195	3813
CRE 158/2016	Endotracheal aspirate	HRPB	Perak	195	3762
CRE 245/2015	Rectal swab	HKL	Kuala Lumpur	938	3679
CRE 341/2015	Urine	HKL	Kuala Lumpur	1947	4057
CRE 400/2016	Endotracheal aspirate	HRPB	Perak	938	3681
CRE 449/2014	Endotracheal aspirate	Temerloh	Pahang	1948	3651
CRE 596/2014	Endotracheal aspirate	HKL	Kuala Lumpur	208	3687
CRE 645/2015	Rectal swab	HRPB	Perak	208	3693
CRE 648/2015	Endotracheal aspirate	HKL	Kuala Lumpur	208	3690
CRE 85/2016	Urine	Temerloh	Pahang	1418	3636
CRE 98/2014	Endotracheal aspirate	Sibu	Sarawak	195	3680
A.baumannii ATCC 17978	ATCC	Control	Control	112	3783

Table 1: *A.baumannii* by Oxford MLST, Hospital origin, Genes and Specimen type by year 2011-2016.

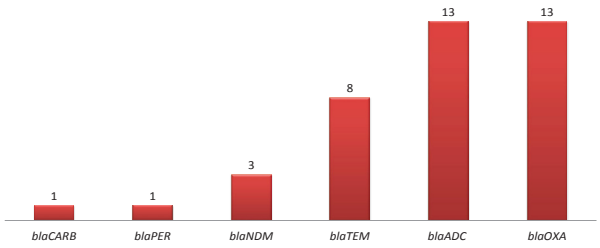


Figure 2: Beta-lactam genes of *A.baumannii* isolates of year 2011-2016.

Discussion

Endotracheal aspirate was the dominant clinical sample source (n=6) and only one isolate was obtained from wound swab. Overall, 5307 encoding genes detected in these isolates, however, only 2893(55%) identical genes shared among isolates. Oxford Scheme of multi-locus sequence typing for *A.baumannii* demonstrated that these 13 isolates belong to 6 different STs, making them genetically diverse. ST195 is the predominant ST, followed by ST208, ST938, ST1418, ST1947 and ST1948. Twenty-nine known antibiotic resistance genes identified but only 20 identical genes harbored in all isolates. We found all 13 Cr-Ab isolates possessed multiple beta-lactamase genes of Ambler Group A, B, C and D. blaOXA-23(n=13) and blaOXA-66(n=11) were the dominant carbapenemase genes families found in these isolates. All isolates harbor blaADC, blaOXA51-like and blaOXA23-like genes. blaTEM3&4(n=7), blaNDM-1(n=3), blaCARB-8(n=1) and blaPER-3(n=1) are amongst other beta-lactamase genes found in this study. SHV, CTX-M, VEB, KPC, VIM, and GES encoding genes were not found. Insertion sequence Aba1 was found upstream to blaOXA-23(n=13), blaOXA-66(n=1) and blaADC(n=11). All blaNDM-1 isolates had ISAba125-mobile genetic elements upstream to the genes.

Conclusion

Multiple genes contribute to antibiotic resistant mechanism. The association of insertion sequence with resistant gene is worrisome and present as an emerging threat to our healthcare settings. Molecular surveillance is essential in implementing policies and prevents the spread Cr-Ab.

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Acknowledgement
This study was supported by the Ministry of Health, Malaysia. Thank you to all Institute for Medical Research staff involved in this study.

POSTER WINNERS AT CONFERENCES

13th Ministry of Health – Academy of Medicine Malaysia Scientific Meeting, National Institute of Health (NIH), Shah Alam, Selangor - 27-29 August 2019

POSTER presenter :

1.) **Best for Biomedical category –** Dr. Alan Khoo See Beng, Head of Cancer Research Centre (CaRC)
Title : *Nasopharyngeal Carcinoma derived Epstein-Barr Virus Variants in Malaysia*

2) **Best for Biomedical category –** Dr. Mohd Ridzuan Mohd Abd Razak (Research Officer) Bioassay Unit, Herbal Medicine Research Centre (HMRC)
Title : *Pre-Clinical Efficacy Evaluation of Free-dried Carica papaya leave juice as dengue alternative treatment*

3) **Best for Public Health category –** Mrs. Noor Afizah Ahmad (Research Officer), Entomology Unit, Infectious Disease Research Centre (IDRC)
Title : *Invading the wAlbB Wolbachia strain for population replacement and control of Aedes borne diseases in AU2, Keramat*

30th National Scientific Conference 2019 in conjuction with Borneo Scientific Meeting 2019 Waterfront Hotel Kuching, Sarawak - << 7 - 8th of October 2019

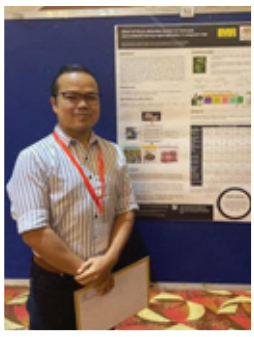
POSTER presenter :

1.) **First Prize –** Ms Elda Nurafnie Ibnu Rasid (Research Officer), Toxicology and Pharmacology Unit, Herbal Medicine Research Centre (HMRC)
Title : *Embryo toxicity Study of Labisa pumila var alata Using Whole Embryo Culture of Sprague Dawley Rats*

2.) **Second Prize –** Mrs. Nor Azrina Norahmad (Research Officer), Bioassay Unit, HMRC
Title : *Inflammatory Cytokine Profiling of Symptomatic Dengue Fever Mouse Model Infected with Clinical Dengue Virus Isolate*

3.) **Third Prize -** Dr Hussin Muhammad (Research Officer), Toxicology and Pharmacology Unit, HMRC
Title : *Effect of Ficus deltoidea Extract on Foetuses Administered during Organogenesis in Pregnant Rats*





BEST POSTER FOR ORIGINAL ARTICLE CATEGORY
MRS NOOR AFIZAH AHMAD, ENTOMOLOGY, IDRC.

P004

Invading the *w*AlbB *Wolbachia* strain for population replacement and control of *Aedes* borne diseases in AU2, Keramat

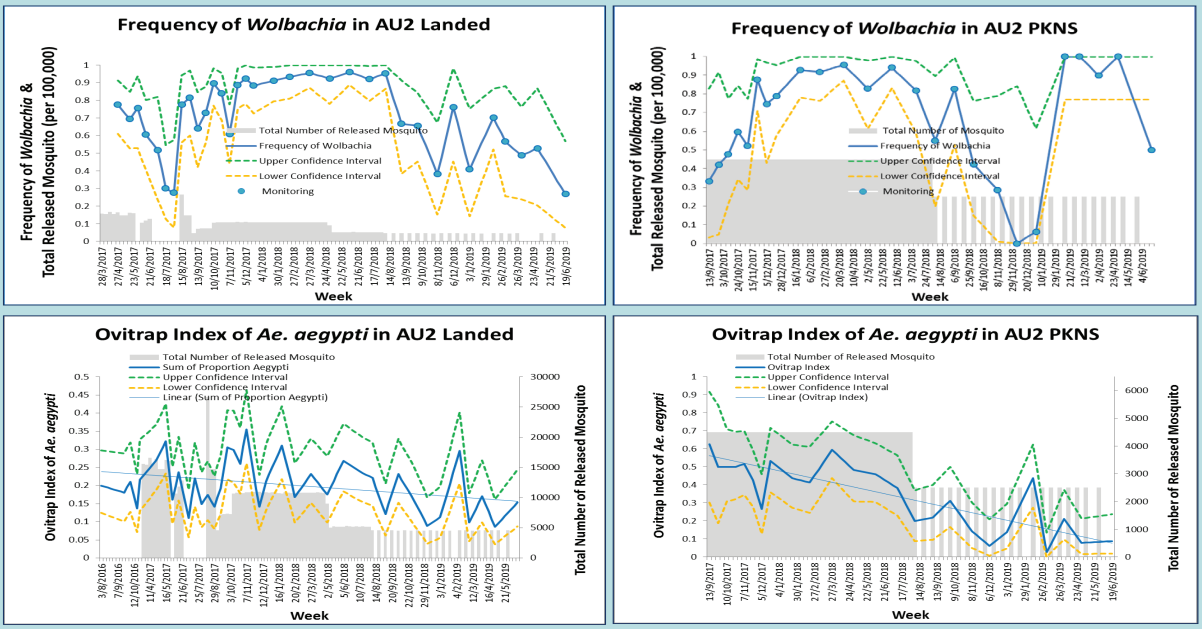
Noor Afizah A, Nazni WA, Cheong YL & Lee HL

Medical Entomology Unit, Institute for Medical Research, WHO Collaborating Centre for Ecology, Taxonomy & Control of Vectors of Malaria, Filariasis and Dengue

Introduction: *Wolbachia* are naturally occurring bacteria found in 60% of insect species including some mosquitoes. However, *Wolbachia* is not found in *Aedes aegypti*. *Wolbachia* infected *Ae. aegypti* can stop the replication of dengue, Zika and chikungunya inside their body and hence stopping disease transmission. The objective of this study is to invade the heat tolerant *w*AlbB *Wolbachia* strain for population replacement and control of *Aedes* borne diseases in a tropical urban setting in AU2, Keramat.

Methodology: *Wolbachia* infected *Aedes aegypti* were released weekly on a pre-determined grid with one cup of 50 mosquitoes released on a grid on ground in two settings; AU2 landed and AU2 PKNS flats. After around 4 weeks of releases, *Wolbachia* frequency monitoring commenced using ovitraps. The resulting eggs were raised to adults and screened for *Wolbachia* presence using real-time PCR-HRM assay. The cumulative dengue cases pre- and post-release were also compared.

Results:



Figures show Wolbachia frequency during and after releases. Release numbers are shown in grey shading; 95% binomial confidence intervals are shown

Discussion:

- The frequency of *Wolbachia* exceeded 80% but subsequently fluctuated following cessation of releases. Immigration of wild mosquitoes from surrounding untreated areas can reduce *Wolbachia* frequency where there is a low population size and relatively weak boundary barriers to mosquito population movement.
- It was found that once *Wolbachia* has existed in the population, a lower release rate can cause *Wolbachia* frequencies to rapidly rise again.
- Densities of adults of target *Ae. aegypti* showed a slight reduction, overall. This is expected given that mating between released males and wild females result in embryo death due to cytoplasmic incompatibility, balancing the population-increasing effects.
- The cumulative dengue cases post-release showed a reduction of at least 64% and 68% at AU2 landed and PKNS flats, respectively.

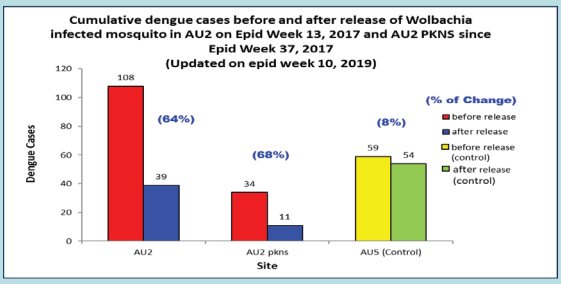


Figure shows cumulative dengue cases in release sites and control site at which no releases going on yet the ordinary dengue intervention is taking place

Conclusion: The results clearly demonstrate the capacity of *Wolbachia* strain *w*AlbB in *Ae. aegypti* to become established in *Ae. aegypti* populations. A good boundary barrier is crucial to maintain the high frequency *Wolbachia* infection in the population. A reduction in dengue cases were also observed. Nonetheless, diverse intervention sites are needed to comprehensively evaluate *w*AlbB effects on dengue transmission in different settings.

ORAL/POSTER WINNERS AT CONFERENCES

Scientific Conference on Obesity, Hotel Istana, Kuala Lumpur - 15 – 16 October 2019

ORAL presenter :

Second Prize for Young Investigator's category –

Ms. Liyana Ahmad Zamri (Research Officer),
Endocrine & Metabolic Unit,
Nutrition, Metabolic and Cardiovascular
Research Centre (NMCRC)
Title : *Impact of weight change on cardiometabolic risk markers in overweight and obese women from low socioeconomic community in a lifestyle intervention study*

21st Islamic Medical Association Malaysia (IMAM) Annual Scientific Conference Grand Riverview Hotel, Kota Bharu, Kelantan << 17 - 19 October 2019

POSTER presenter :

Best poster :

Mrs Nik Aishah Nik Hitam
(Science Officer), Biochemistry Unit,
Specialiased Diagnostic Centre (SDC)
Title : *Verification of Quantitative Measurement of Urinary Creatinine Enzymatic Method Kit by DIRUI CS-T240*

Genomic Landscape of BCR-ABL Kinase Domain Mutation in Chronic Myeloid Leukemia Patients with Imatinib Resistance

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INTRODUCTION

- Chronic Myeloid Leukemia (CML) is a clonal myeloproliferative disorder involving the pluripotent hematopoietic stem cell compartment.
- It is associated with Philadelphia Chromosome, a reciprocal translocation between chromosomes 9 and 22, t(9;22) (q34;q11) which results in constitutively active breakpoint cluster region-Abelson (BCR-ABL) tyrosine kinase and plays a central role in the pathogenesis of CML.
- Discovery of imatinib mesylate (IM) as targeted BCR-ABL protein kinase inhibitor (TKI) has resulted in its use as frontline therapy, which brought tremendous improvement in the management of CML.
- However, emergence of mutation in the BCR-ABL kinase domain (KD) impairs IM binding capacity thus contribute to IM resistance.
- Our study aims to determine the genomic landscape of BCR-ABL KD mutations in these patients, to determine the prevalence of these mutations in our population and to identify novel, pathological mutations.

MATERIALS AND METHODS

- A cohort of 86 CML patients with IM resistance was enrolled in this study.
- They were recruited from Ministry of Health Hospitals in 2016 – 2018.
- The isolated RNAs were reverse-transcribed into cDNA using Reverse Transcriptase kit (Qiagen, Germany) according to the manufacturer's instructions.
- The reverse transcriptase (RT) PCR assay was performed for BCR-ABL gene amplification.
- The first PCR was amplified from synthesized cDNA using a set of designated primers of tyrosine kinase domain of the BCR-ABL p210 transcript.
- The second PCR was then amplified using three pairs of ABL KD designated primers.
- All mutations were characterized using Sanger sequencing.
- The discovered mutation was verified according to standard amino acid substitution nomenclature.

RESULTS AND DISCUSSION

- Our subjects consisted of 48 male and 28 female patients with CML at a median age of 46.5 years (range: 13 - 81 years).
- Majority were Malays (40/86), followed by Chinese (30/86), Indians (9/86) and others (7/86).
- BCR-ABL KD mutations were observed in 23 patients (26.7%) (Table 1).
- Fifteen different types of mutations have been identified (Table 2).
- Amongst all mutations identified, Y253H is the most common mutation (Table 2).
- Spectrum of mutation varies between patients.
  - 18/23 patients were found to have single mutation
  - 5/23 patients have multiple mutations
- We also discovered that two patients have silent mutation at codon 389 and 401.
- Interestingly, we discovered 3 novel mutations:
  - M290R
  - K285I
  - K357T

Table 1: BCR-ABL KD mutation in CML patients with IM-resistance

BCR-ABL KD mutation status, n = 86	
Presence of mutation	23 (26.7%)
Absence of mutation	63 (73.3%)
Disease status in patients with mutation, n=23	
Chronic phase	10 (43.5%)
Accelerated phase	8 (34.8%)
Blast phase	5 (21.7%)

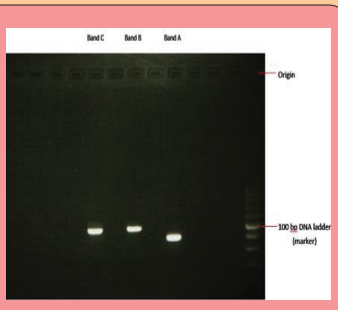

Figure 1: Gel electrophoresis showing presence of bands after second round of RT-PCR with 3 set of different primers in a patient.
Band A = fragment A present at 400 bp.
Band B = fragment B present at 500 bp
Band C = fragment C present at 500 bp.

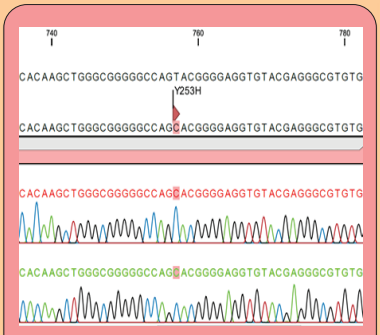

Figure 2: Sequencing chromatogram of a patient with Y253H mutation showing substitution of T → C at 757 cDNA position.

This mutation leads to the alteration of amino acid tyrosine (Y) with amino acid histidine (H) at codon 253.

Table 2. BCR-ABL KD mutation spectrum in CML patients with IM-resistance.

cDNA position with Nucleotide Change	Amino Acid Substitution (Gen Bank no. X16416 (ABL)	No. of Patients with Mutation	ABL Kinase domain
Single Mutation			
757 T>C	Y253H	6	P loop
763 G>A	E255K	1	P loop
799 A>G	T267A	1	other mutation
931 T>A	F311I	4	IM binding site
944 C>T	T315I	2	IM binding site
951 C>A	F317L	1	IM binding site
1075 T>G	F359V	1	C loop
1075 T>A	F359I	1	C loop
1203 C>T	F401F	1	A loop
Multiple Mutations			
757 T>C & 869 T>G	Y253H / M290R*	1	P loop / αC-helix
757 T>C & 1167 A>G	Y253H / T389T	1	P loop / A loop
854 A>T & 1375 G>A	K285I* / E459K	1	αC-helix / other mutation
1070 A>C & 1076 T>G	K357T*/ F359C	1	C loop
757T>C, 859 G>A & 1195 G>A	Y253H / A287T / A399T	1	P loop/ αC-helix / A loop

*= Novel mutation. Genbank accession number X16416.

CONCLUSION

- Mutation analysis of BCR-ABL KD is recommended in CML patients with IM-resistance to identify patients at risk of disease progression.
- Knowing the exact mutations responsible for IM resistance will help clinician to select the most suitable TKIs for CML patients and improve patients management.
- Early detection of such mutations may allow timely treatment intervention to prevent or overcome resistance.
- Therefore, this test should be offered as diagnostic platform to guide therapy for precision medicine.

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